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INVITED REVIEW

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Rubella virus chronic inflammatory disease and other unusual viral phenotypes in inborn errors of immunity

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Summary

Infectious susceptibility is a component of many inborn errors of immunity. Nevertheless, antibiotic use is often used as a surrogate in history taking for infectious susceptibility, thereby disadvantaging patients who present with viral infections as their phenotype. Further complicating clinical evaluations are unusual manifestations of viral infections which may be less familiar that the typical respiratory viral infections. This review covers several unusual viral phenotypes arising in patients with inborn errors of immunity and other settings of immune compromise. In some cases, chronic infections lead to oncogenesis or tumor-like growths and the conditions and mechanisms of viral-induced oncogenesis will be described. This review covers enterovirus, rubella, measles, papillomavirus, and parvovirus B19. It does not cover EBV and hemophagocytic lymphohistiocytosis nor lymphomagenesis related to EBV. EBV susceptibility has been recently reviewed. Our goal is to increase awareness of the unusual manifestations of viral infections in patients with IEI and to describe treatment modalities utilized in this setting. Coincidentally, each of the discussed viral infections can have a cutaneous component and figures will serve as a reminder of the physical features of these viruses. Given the high morbidity and mortality, early recognition can only improve outcomes.

KEYWORDS
CEMA, immunodeficiencies, inborn errors of immunity, measles, rubella

1 | INCREASED VIRAL SEVERITY

Inborn errors of immunity (IEI) are a diverse set of over 500 conditions either altering or compromising the adaptive immune system and/or the innate immune system.[1] Consequently, immune responses to viruses can be altered (e.g., hyperinflammation) or compromised in IEI. Increased severity of viral infections is expected in patients with T-cell defects. The most extreme example of this is respiratory viral infections occurring in infants with severe combined immunodeficiency (SCID) whereby resolution typically occurs only after successful engraftment post hematopoietic cell transplant. In patients with the defects of T-cell production or function, viral infections can be both more severe and prolonged. Very severe viral infections have also been demonstrated in disorders of the innate immune system affecting the Type I interferon pathway.[2–5] A general increase in the severity of the viral infection is not the purview of this review article nor is coverage of hemophagocytic lymphohistiocytosis, often a diagnostic conundrum,[6,7] because it has been reviewed comprehensively recently as has EBV susceptibility.[8–12] The goal of this review is to cover distinct or unusual phenotypes caused by viral infections in people with IEI.

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2 | VIRUSES CAUSING A DISTINCT PHENOTYPE IN PATIENTS WITH IEI

The clinical manifestations of any given viral infection reflect a complex interplay between direct viral affects, often including cytopathic effects, and the host responses to the viral infection. In IEI, it is never the case that all components of host defense are compromised. Therefore, host responses to the virus can exhibit abnormal compensatory mechanisms or the revealing of alternative host responses that are typically less obvious in a normal response. The five viruses reviewed in the subsequent sections demonstrate different types of compensatory and alternative responses as well as failure to contain or eradicate the virus. Table 1 reviews the frequency of the viruses reported to a national registry called USIDNET in different IEI without reference to the phenotype of the infection.[13] It can be seen that viral infections in general are an abundant cause of morbidity across IEIs. Note that each virus is enriched in different types of IEI with enterovirus enriched in agammaglobulinemia and herpes simplex enriched in common variable immunodeficiency. Note that warts and papillomavirus were reported separately because not all cases had viral detection. Therefore, a focus on unusual phenotypes of viral infections represents an important clinical topic.

TABLE 1 Viral infections in patients with IEI reported to USIDNET.

Infections	Distinct count of patients
Enterovirus	
Agammaglobulinemia	15
Charge syndrome	1
Chronic granulomatous disease	8
Combined immune deficiency	2
Common variable immune deficiency (CVID)	11
DiGeorge syndrome	5
HLH, including XLP and pigmentary disorders	2
Hyper IgE syndrome	1
Hyper IgM syndrome	5
Hypogammaglobulinemia	3
Immune dysregulation	8
Immunodeficiency with myelodysplasia (GATA2 and others)	2
Mucocutaneous candidiasis	4
Other immune deficiency—known cause	1
Predisposition to severe viral infections	2
Severe combined immune deficiency (SCID)	26
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	3
Susceptibility to mycobacteria (MSMD)	1
Transient hypogammaglobulinemia of infancy with normal numbers of B cells	1
Wiskott–Aldrich Syndrome	3
Herpes simplex	
Agammaglobulinemia	8
Autoimmune lymphoproliferative syndrome (ALPS)	2
Chronic granulomatous disease	12
Combined immune deficiency	12
Common variable immune deficiency (CVID)	80
Ectodermal dysplasia with immunodeficiency (NEMO and others)	4
HLH, including XLP and pigmentary disorders	3
Hyper IgE syndrome	8
Hyper IgM syndrome	7
Hypogammaglobulinemia	6
IgG subclass deficiency	1
Immune dysregulation	14
Immunodeficiency with myelodysplasia (GATA2 and others)	7
Leukocyte adhesion deficiency	1
Mucocutaneous candidiasis	12
Other immune deficiency—known cause	2

2.1 | Enterovirus

2.1.1 | Viral characteristics

Enteroviruses belong to the virus family *Picornaviridae* (small RNA virus). The *Enterovirus* genus currently consists of 12 species, 7 of which are viruses that infect humans: *Enterovirus A*, *B*, *C*, *D*, and *Rhinovirus A*, *B*, and *C*.[14,15] New enteroviruses are assigned names by their species letter and then the new number (e.g., enterovirus D68). Enteroviruses are common and the prevalent enteroviral types vary each year.[16] In a normal host, most infections last 2–3 weeks and are either asymptomatic or present as a mild febrile illness with either respiratory symptoms or gastrointestinal symptoms. Severe disease including myocarditis, pancreatitis, myopathy, and meningitis occurs in apparently normal hosts. Newborns are particularly susceptible to serious disease such as neonatal enteroviral sepsis, myocarditis, pericarditis, meningitis, encephalitis, acute flaccid myelitis or paralysis, and poliomyelitis presumably due to their immunologic immaturity. In addition to host factors driving severe disease, some specific enterovirus types such as echovirus 6 (E6), E9, and E30 are associated with aseptic meningitis; E11 is associated with enteroviral sepsis presenting as hepatitis–hemorrhage syndrome; and CVB5 is associated with myocarditis. However, each virus can be associated with several disease presentations and all enteroviral types have some capacity to be neurotropic.[17]

TABLE 1 (Continued)

Infections	Distinct count of patients
Predisposition to severe viral infections	4
Severe combined immune deficiency (SCID)	10
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	2
TLR pathway abnormality	1
Wiskott–Aldrich syndrome	17
Measles	
Agammaglobulinemia	1
Common variable immune deficiency (CVID)	2
Other immune deficiency—known cause	1
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	1
Wiskott–Aldrich syndrome	2
Papillomavirus	
Agammaglobulinemia	1
Autoimmune lymphoproliferative syndrome (ALPS)	1
Chronic granulomatous disease	1
Combined immune deficiency	11
Common variable immune deficiency (CVID)	25
Complement deficiency	1
DiGeorge syndrome	1
Hyper IgE syndrome	1
Hyper IgM syndrome	3
Hypogammaglobulinemia	1
Immune deficiency with syndromic features (not otherwise listed)	1
Immune dysregulation	5
Immunodeficiency unknown cause	1
Immunodeficiency with myelodysplasia (GATA2 and others)	25
Leukocyte adhesion deficiency	1
Mucocutaneous candidiasis	2
Neutropenia	1
Other immune deficiency—known cause	1
Predisposition to severe viral infections	12
Severe combined immune deficiency (SCID)	12
Wiskott–Aldrich syndrome	7
Parvovirus	
Combined immune deficiency	1
Common variable immune deficiency (CVID)	3
Hyper IgE syndrome	1
Hyper IgM syndrome	3
Immunodeficiency with myelodysplasia (GATA2 and others)	1
Leukocyte adhesion deficiency	1

TABLE 1 (Continued)

Infections	Distinct count of patients
Other immune deficiency—known cause	1
Severe combined immune deficiency (SCID)	1
Rubella	
Agammaglobulinemia	1
IgA deficiency	1
Predisposition to severe viral infections	1
Wiskott–Aldrich syndrome	1
Warts	
Agammaglobulinemia	2
Ataxia telangiectasia	2
Autoimmune lymphoproliferative syndrome (ALPS)	1
Chronic granulomatous disease	9
Combined immune deficiency	12
Common variable immune deficiency (CVID)	49
Complement deficiency	1
Ectodermal dysplasia with immunodeficiency (NEMO and others)	1
Hyper IgE syndrome	4
Hyper IgM syndrome	3
Hypogammaglobulinemia	6
Immune dysregulation	9
Immunodeficiency unknown cause	1
Immunodeficiency with myelodysplasia (GATA2 and others)	19
Leukocyte adhesion deficiency	2
Mucocutaneous candidiasis	3
NK cell defect	1
Other immune deficiency—known cause	4
Predisposition to severe viral infections	16
Severe combined immune deficiency (SCID)	25
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	3
Wiskott–Aldrich syndrome	10
Grand total	534

2.1.2 | Neurologic disease in XLA

In the early 1970s, enteroviral infections were first described in X-linked agammaglobulinemia (XLA). Approximately 15%–20% of XLA patients were infected with generally poor outcomes.[18,19] The first descriptions of chronic enteroviral meningoencephalitis (CEMA) began to appear in the 1970s and described acute flaccid paralysis related to live polio vaccine administration or meningoencephalitis with non-polio enteroviruses.[20–22] Outcomes were poor with only 5% having a good outcome.[19]

Today, this is an uncommon but still tragic complication in XLA with 3% of patients in the US registry, USIDNET, having confirmed enteroviral infections (Table and Refs [23,24]). In the ESID registry, 1% had reported enteroviral meningoencephalitis and the LASID registry had 4% of patients with XLA with meningoencephalitis. Therefore, enteroviral disease is an uncommon complication in XLA but the severity is high with many fatalities. The age of onset of enteroviral disease in XLA ranges from infancy to 50 years of age and the phenotypes include classic CEMA, arthritis, hepatitis, dermatomyositis, polyradiculitis, and myocarditis. In some cases, patients were not on immunoglobulin treatment but among treated patients, the average IgG was only 300 mg/dL.[19] Higher IgG levels appear to confer some protection, although it is not clear that there is any level that confers complete protection.[25]

CEMA is the most severe of the presentations. Patients present with loss of motor and cognitive milestones with progression over weeks or months before diagnosis.[19,26] Other presentations include an acute encephalomyelitis, flaccid paralysis, or an acute or chronic myelopathy and whether these phenotypes are driven by the virus or by host responses is not known.[27,28] The neurologic features can wax and wane over time, but most patients typically exhibit is a slow decline and death within 2 years.[19]

2.1.3 | Diagnosis

Once there is a clinical suspicion, it is important to activate a plan for diagnosis. MRI is usually the first modality invoked. Symmetric white matter hyperintensities (typically bright on T2 without associated diffusion weighted imaging signal or contrast enhancement) are the most typical finding (Figure 1A); however, early MRI results can be completely normal.[27,30,31] Leptomeningeal contrast enhancement is also typical.[27,31–33] Late cases will exhibit atrophy (Figure 1B,C).

Lumbar punctures are usually performed in the setting of suspected CEMA. A lymphocytic pleocytosis with lymphocyte counts in the 40–400 range are common but not invariant. Protein is usually elevated with low glucose.[26] As is true for the MRI, the CSF may be completely normal early in the disease course. Enterovirus is usually detected by PCR from CSF[34–36] but a brain biopsy should be considered if there is a high index of suspicion, but CSF PCR is negative. While CSF PCR has high sensitivity for epidemic enteroviral meningitis in the general population, the sensitivity appears lower in CEMA. In some cases, rectal or throat swabs have been positive for enterovirus; however, caution must be used in interpretation as these may be distinct isolates from the brain. Unbiased high throughput sequencing has successfully identified enteroviruses and other pathogens in the brains of patients with a CEMA-like picture. Hence the concern regarding correct identification of the pathogen. Aichivirus and astrovirus have been identified in boys with XLA and

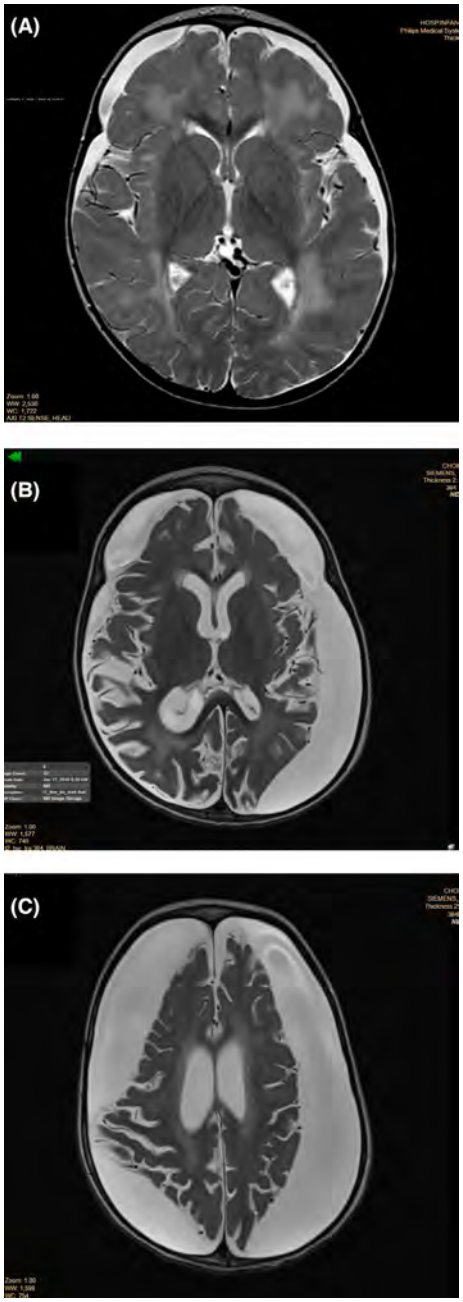


FIGURE 1 MRI findings in chronic enteroviral meningoencephalitis in X-linked agammaglobulinemia. (A) MRI performed near the time of presentation at 2.5 years of age with mild ataxia showing confluent periventricular and subcortical white matter T2 signal abnormality/hyperintensity, also affecting the subcortical U fibers. Subdural CSF collections can be observed bilaterally. Panels (B,C) are from three years later and interval progression can be seen. The subdural collections have markedly increased. The white matter signal intensities were unchanged. Panel (A) and panels (B,C) were performed on different MRI. All panels are T2 images. Clinically, he was significantly more neurologically compromised. These images are from a previously published personal case but the images themselves have not been published.[29]

meningoencephalitis with a similar clinical picture.[37] Therefore, it cannot be assumed that all meningoencephalitis is due to enteroviral infection in XLA. Indeed, the differential diagnosis for CEMA includes JC virus, measles, HIV, cytomegalovirus, arboviruses, and herpes viruses, as well as atypical bacterial infections, tick-borne infections, chronic fungal infections, autoimmune disorders, and reactions to IVIG.[38]

2.1.4 | Other conditions with CEMA and enteroviral susceptibility

There have been sporadic cases of patients with other forms of agammaglobulinemia, SCID, and hyper IgM developing CEMA. Today, in the United States, most infants with SCID are diagnosed through newborn screening and exposures to enterovirus are unlikely. The possibility of newborn screening for XLA may impact XLA outcomes by preventing some CEMA.[39,40] The rarity of CEMA in non-XLA conditions suggests that the pathogenesis is not entirely related to lack of antibody and either lack of BTK or B cells is more likely to drive disease.

There is currently an evolving recognition of susceptibility to enterovirus among people treated with rituximab, a B cell depleting agent widely used for lymphoma, multiple sclerosis, and systemic lupus erythematosus.[41–54] The population treated with rituximab has generally had a more acute presentation of disseminated disease or meningoencephalitis compared to the slow onset seen in XLA; however, late relapses and late relapses in different organs have been observed suggesting incomplete clearance even in the setting of clinical improvement. Patients who have developed CEMA after rituximab have often had multiple simultaneous immune suppressive therapies, making it difficult to ensure that susceptibility to CEMA was driven exclusively by rituximab treatment. Nevertheless, CEMA and acute disseminated enteroviral disease are rare in patients undergoing chemotherapy for solid organ malignancies suggesting that not all immune suppression is associated with susceptibility. Newer B-cell depleting agents have been used much less extensively but surveillance for CEMA is warranted and the new BTK inhibitor class of drugs will require yet more vigilance. One patient with disseminated enteroviral disease after combined therapy with rituximab and ibrutinib suggests caution is appropriate.[55]

2.1.5 | Management

Most of the cases of patients on B-cell depleting medications have been successfully treated with high-dose IVIG and supportive care although a mortality rate of 37% has been reported in this setting.[56] In XLA, outcomes vary widely.[29] In a recent USIDNET report, there was a single death from viral meningoencephalitis[23] but in a worldwide survey, CEMA occurred in 4% of patients overall[57] and the mortality rate of published cases corresponded to the rate of meningitis/encephalitis, suggesting enteroviral disease is a major driver of mortality (Figure 2). Therefore, there is great need for therapeutics directed at enterovirus for this population.

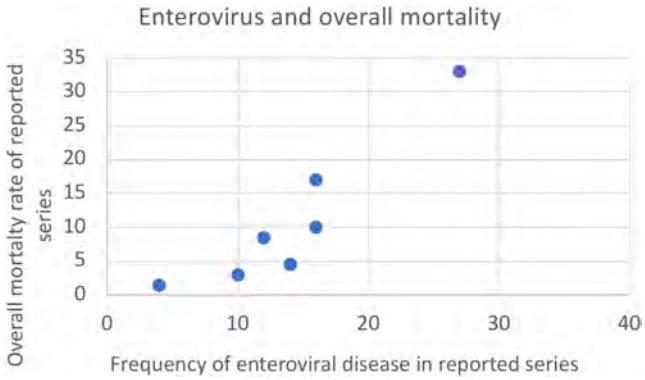


FIGURE 2 Correlation of enteroviral cases reported and mortality from different countries. Publications reported both and including a significant sample size were included.[57]

High-dose intravenous immunoglobulin (IVIG) has a reasonable success rate[25,26,58,59] and intrathecal immunoglobulin has also induced multiple remissions.[19,26,33,60,61] Severe side effects with intrathecal therapy are common, limiting its utility.[26,58] Generic antiviral therapy with interferon alpha,[59] intrathecal interferon beta,[60] ribavirin,[58,62] and cidofovir have also been used with uncertain efficacy.[63] Specific anti-enteroviral therapy was pioneered with pleconaril, which appeared to induce remission in several patients.[63–67] Pocapavir, the successor to pleconaril, is under development by ViroDefense Inc. and appears to have efficacy in case reports although not all enteroviruses are equally susceptible.[68–70] Pocapavir can sometimes be obtained directly from ViroDefense but an alternative with a few reports of efficacy is fluoxetine. Developed as an antidepressant, it inhibits the enterovirus 2C protein, which is involved in viral RNA replication.[71,72]

Hematopoietic cell transplantation is seldom performed in the United States for XLA although other countries have had success with this as a definitive treatment.[73] A health care economic study also found favorable economics for the use of transplant for XLA.[74] There are no reports of cure of CEMA after transplant but it is a reasonable consideration given the poor outcomes with antiviral approaches. Unknown at this time is whether there is a CNS-intrinsic BTK deficiency critical for CEMA pathogenesis.

2.2 | Rubella

2.2.1 | Viral characteristics

Rubella virus (RuV) is classified as a member of the genus *Rubivirus* in the *Matonaviridae* family. The RuV particle consists of a 10 kb single-stranded plus-sense genomic RNA packaged into a viral capsid formed by C protein surrounded by the lipid envelope with two spike viral glycoproteins, E1 and E2. The E1-E2 heterodimer is responsible for binding to cellular receptor(s) and endocytosis and is critical for

FIGURE 3 Features of rubella. (A) Blueberry muffin rash in CRS. (B) Rubella arthritis. (C) The classic rubella rash in siblings. (D) The public health initiative to encourage vaccination to prevent CRS in the 1960s. All photos are from the CDC public health photo library.

humoral immune recognition. E1 represents the primary target for neutralizing antibodies. There are likely multiple entry receptors for RuV although the one for which the best evidence exists is myelin oligodendrocyte glycoprotein (MOG).[75]

Humans are the only known species naturally infected with RuV. Typically, the virus enters the nasopharynx with subsequent viremia after respiratory-to-respiratory transmission via droplets. Viremia is associated with the characteristic 3-day rash (Figure 3). Young children often have no symptoms or mild symptoms without fever.[76] Older children and adults are more likely to experience malaise, fever, and anorexia. The most common complications include elevation of liver function tests and arthritis/arthralgia. As many as 52% of adult women newly infected with RuV have arthritis/arthralgia.[77] Specific joints can include fingers, wrists and knees. The arthritis most often resolves spontaneously as is typical for a viral arthritis (Figure 3).

2.2.2 | Congenital rubella syndrome

In the late 1960s an enormous public health program dedicated to the development of a rubella vaccine arose to prevent the epidemic of congenital rubella syndrome (CRS) in the United States (Figure 3). The famous actress Gene Tierney is thought to have had a baby in 1943 affected with CRS, thereby triggering a mental health decline. The fearsome effects of CRS are now mostly relegated to textbooks in the United States although cases continue in parts of Asia, Africa, and other countries without strong vaccine programs.[78] The most common features of CRS depend on the timing of infection but often include heart disease with pulmonary artery stenosis as a characteristic feature, congenital cataracts, microphthalmos, glaucoma, hearing impairment, developmental delay, and microcephaly. Babies can be born with features strongly associated with intrauterine infection such as blueberry muffin rash (Figure 3), hepatosplenomegaly, and thrombocytopenia. Development of the immune system is often impacted in CRS-affected infants. Retarded development of the thymus, decreased CD4/CD8 ratios, decreased activity of NK cells, and reduced number of CD4+ and CD8+ T cells have been reported in some CRS patients leading to impaired cellular immune responses.[79–81] IgM is often elevated, consistent with most intrauterine infections.

2.2.3 | Inflammatory diseases with rubella occurring in the general population

Rubella encephalitis is a feared but uncommon complication of acute infection. In this condition, neurologic features usually appear with the rash. Seizures are the most common feature, and the CSF protein is usually elevated with a modest cell count. Autopsy studies have revealed diffuse neuronal degeneration, edema, and perivascular lymphocytic infiltrates without clear demyelination.[82]

A distinct neurologic phenotype, rubella progressive panencephalitis, has been described after congenital infection. After a stable period of approximately a decade, the patients exhibit neurologic deterioration and seizures.[83] Elevated CSF protein and IgG with high titers of antibody to rubella virus are diagnostic in the appropriate clinical setting. These rare patients suggest subclinical persistence of RuV after CRS or early childhood infection.

Fuchs heterochromatic cyclitis (FHC) is an anterior uveitis leading to color change in the iris. It usually occurs in the third and fourth decades of life and most patients are asymptomatic. It is typically a

disease that strikes only one eye, thereby causing discordant iris colors in the two eyes.[84] Today FHC is most often secondary to the vaccine strain of RuV but in earlier years, it was more often seen after early life natural infection.[85–87] FHC also suggests that the virus may live in a reservoir after acute infection, emerging later in life. Neither rubella progressive panencephalitis nor FHC are thought to occur specifically in people with IEI.

2.2.4 | Chronic rubella infections in people with IEI

Vaccine strain rubella virus causing cutaneous inflammation was initially reported in 2014.[88] To date, nearly 90 RuV-associated cases have been reported in the literature (reviewed in Ref. [89]) and we have studies over 100 cases. The typical picture of the inflammatory lesions are displayed in Figure 4 with the immunofluorescence testing for RuV used diagnostically at the Centers for Disease Control. Additional studies have defined the types of immunodeficiencies and the poor response to therapy.[88,90,91] Generally significant T-cell compromise is a risk factor.[92] Inflammatory lesions occur throughout the body, but cutaneous inflammation is the most commonly reported (Figure 5A). The timing of granuloma onset appears to depend on the IEI type ranging from 3 weeks to 57 years after MMR vaccination (Figure 5B). The virus has been found in neutrophils and/or macrophages and most often the tissue sites have granulomas[92] (Figure 5C). The recovered RuV have mutated genomic sequences with up to 3% nucleotide substitution relative to the vaccine strain and have therefore been referred to immunodeficiency-related vaccine-derived rubella viruses (iVDRV).[93] Most iVDRVs contain mutated B- and T-cell epitopes suggesting a possible evasion mechanism of vaccine-induced immunity for the maintenance of RuV persistence. Live virus has been recovered and the mutations appear to dictate tissue-specific growth patterns.[93]

Recently reported immunohistological analysis of the iVDRV-associated lesions shows different inflammatory patterns.[92] Most cutaneous granulomas (75%) were non-necrotizing or necrotizing granulomas with focally aggregated RuV capsid present in M2 macrophages. An additional pattern found in 25% of cutaneous granulomas had rubella capsid in neutrophils, typically associated with central necrosis. In other organs, the patterns were quite different with poorly organized granulomas and mixed infiltrate with rubella capsid located primarily in neutrophils. There was no association between specific granuloma patterns and the specific IEI. All samples had a substantial presence of T cells (Figure 5D) even though most individuals had low T-cell counts or defective T-cell cytotoxicity.

While iVDRV-induced inflammation is most often reported in patients with immunodeficiencies, similar pathologic processes have been seen in people who are apparently normal hosts and in people infected with wild-type RuV.[94,95] Thus, this rubella-associated inflammatory disease is not limited to those who are immunodeficient or those who have been vaccinated. Equally important is consideration of settings where iVDRV disease is not observed. It has not been observed in patients undergoing hematopoietic cell transplant nor chemotherapy for non-IEI patients. These settings can be profoundly immune suppressive but importantly are time limited. These clinical observations inform on our model for the development of disease (Figure 6). The T-cell repertoire at the time of exposure may be sufficient to control acute disease or live vaccine exposure and RuV enters into an unknown reservoir suggested by rubella progressive panencephalitis, FHC, and the delay in development if disease in patients with IEI. Compromised control due to T-cell dysfunction and the gradual acquisition of mutations that facilitate persistence and escape contribute to the emergence from the reservoir. Myeloid cells carry RuV and for reasons incompletely understood tend to emerge in the skin where imperfect immune control and possibly viral characteristics drive the granulomatous process (Figure 6).

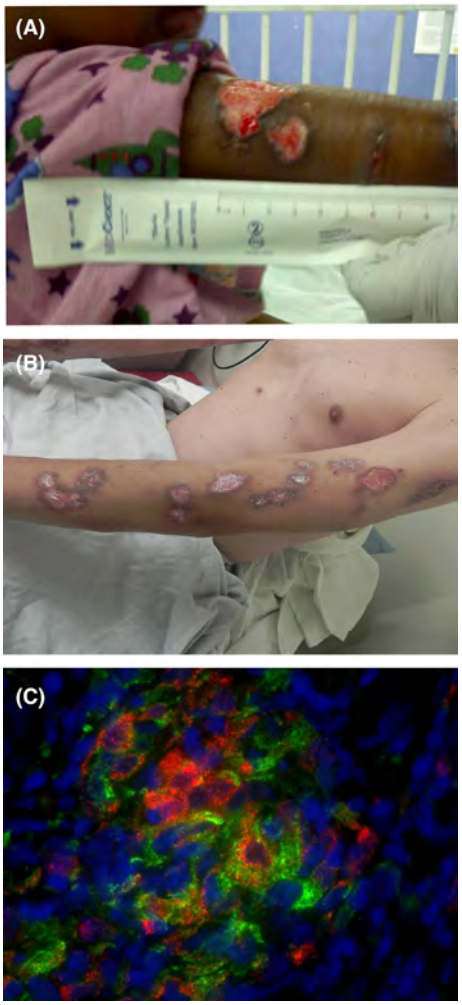


FIGURE 4 Chronic rubella causing cutaneous inflammation. (A) An infant with ataxia telangiectasia and RV+ cutaneous granulomas (photo curtesy of Dr. James Treat). (B) An adult with CVID and RV+ cutaneous granulomas (photo courtesy of Dr. Misha Rosenbach). (C) Immunofluorescence of RV capsid protein (Red), CD206 M2 macrophage marker (green), and DAPI (blue). The immunofluorescence in panel C is from the patient in panel B.

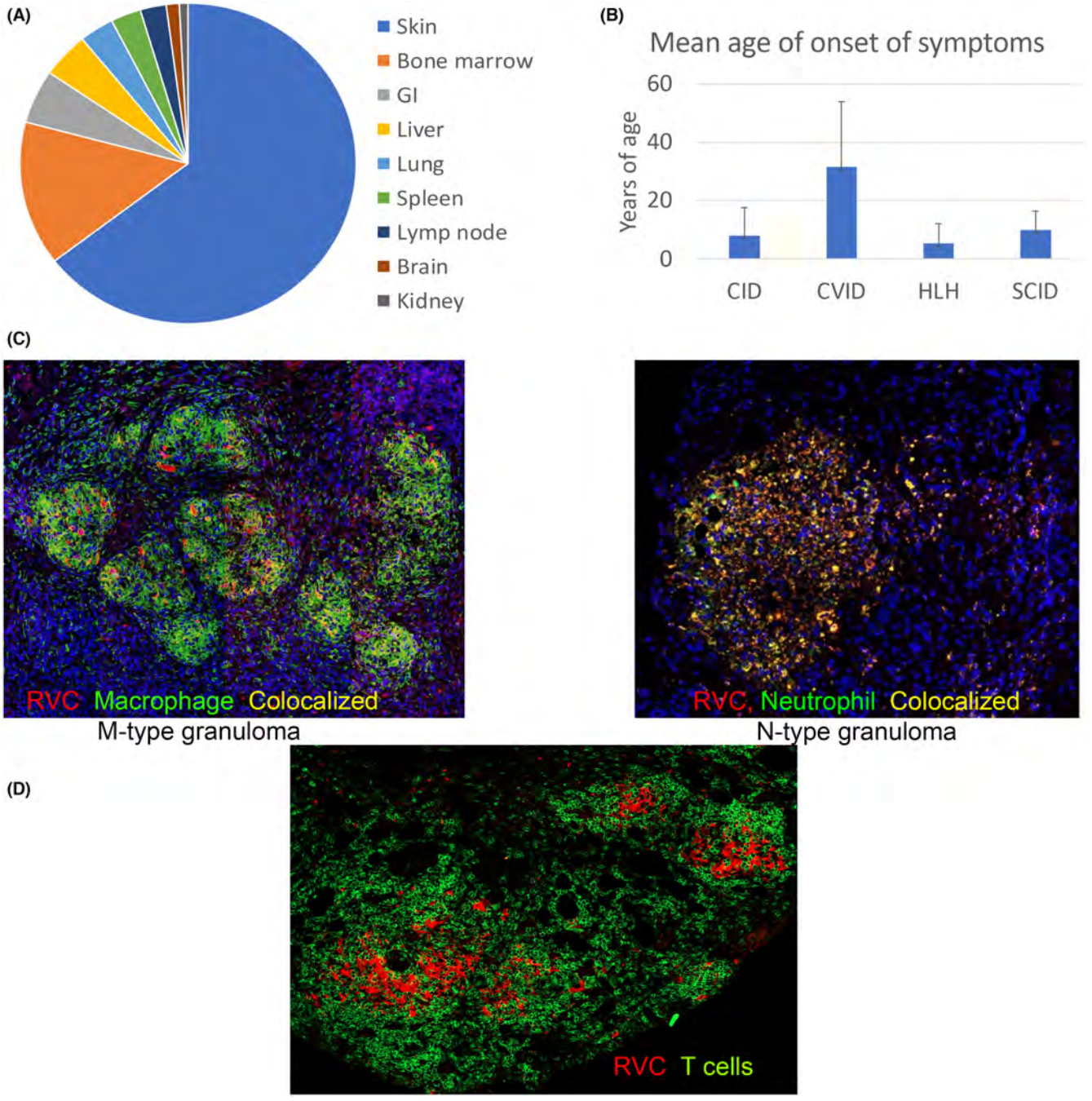


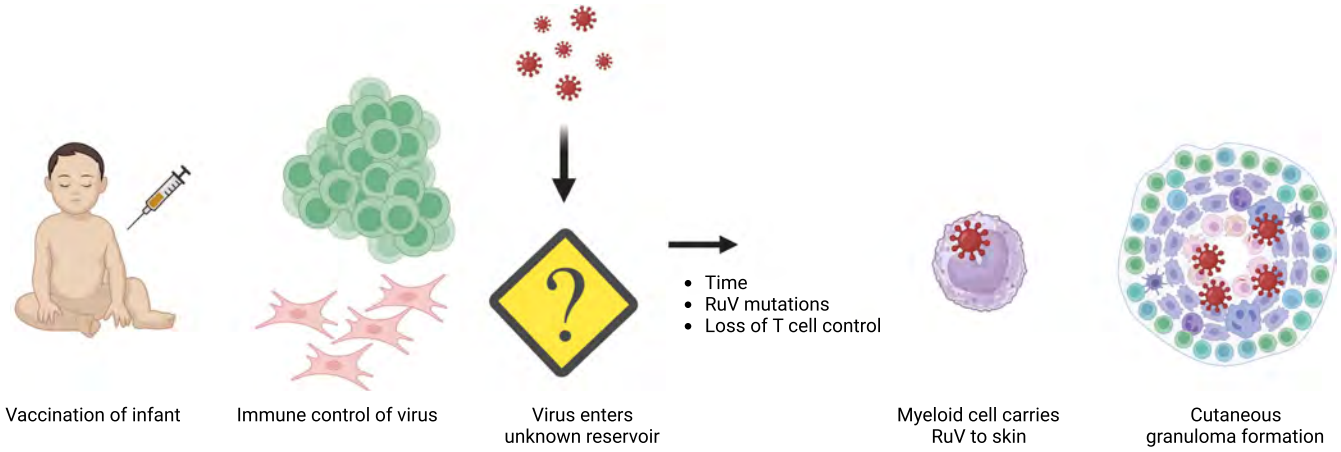
FIGURE 5 Chronic rubella features in IEI. (A) 240 samples submitted to the CDC with positive detection of RuV were distributed across different organs. (B) The age of onset from 75 patients with age of onset reported was categorized according to combined immunodeficiency (CID), common variable immunodeficiency (CVID), hemophagocytic lymphohistiocytosis (HLH), or severe combined immunodeficiency (SCID). Three patients are not included as they represented single cases. The bars indicate the mean and the error bars indicate standard deviation. (C) Granulomas are categorized as M-type with macrophage infection or N-type with neutrophil infection. Not shown are some cases where both macrophage and neutrophil infection were observed in the same granuloma. (D) Although myeloid cells harbor RuV, T cells (green) are always seen surrounding the infected myeloid cells.

2.2.5 | Diagnosis

Currently, the diagnosis of chronic rubella is performed by RT-PCR of affected tissues, nasopharyngeal swabs, oropharyngeal secretions, and urine. RuV has also been detected through immunofluorescence for rubella capsid[85] and unbiased metagenomic screens for pathogens.[96]

2.2.6 | Management

Treatment outcomes have been disappointing. Nitazoxanide and ribavirin have activity against RuV and iVDRV in vitro but use in humans has demonstrated modest efficacy.[97–99] The best outcomes have been with hematopoietic cell transplantation although not all



Model for iVDRV-driven inflammatory disease

FIGURE 6 Model of emergence of iVDRV-associated inflammatory disease. In this model, there is initial immune control of the vaccine strain or wild-type RuV and entry into an unknown reservoir. Emergence from the reservoir depends on both viral intrinsic effects and loss of immune control which occurs more rapidly in settings of severely limited T-cell function or a compromised T-cell repertoire (produced in Biorender).

patients are candidates for this intervention.[97] A recent report of nucleoside analogs with anti-rubella activity suggests direct virus-targeting treatment could be possible.

2.3 | Measles

2.3.1 | Viral characteristics

Measles is a negative polarity RNA virus, a member of the *Paramyxoviridae* family, and the *morbillivirus* genus. The genome includes six genes leading to eight viral proteins. The virus has a helical appearance by electron microscopy and its high stability means it survives on surfaces for up to 2 h. Its mode of transmission is mainly from person to person through droplets, initially infecting respiratory epithelium.[100] The H glycoprotein of the virus binds to alveolar macrophages and dendritic cells that express the measles virus receptor SLAM, also called CD150.[101,102] These infected cells transmit the virus to bronchus-associated lymphoid tissues and/or draining lymph nodes. The virus also proliferates in CD150-expressing B and T lymphocytes. Infected tissues exhibit inflammation and multicellular giant cells with inclusion bodies. Measles is a state of significant immune compromise due to viral proteins V and C that suppress host interferon production and facilitate its replication.[103]

The prodromal phase predates the rash and lasts 4–6 days. Prodromal symptoms include fever, malaise, nasal congestion, conjunctivitis, palpebral edema, and dry cough. Koplik spots, located in the buccal mucosa appear during the prodrome (Figure 7). The second phase is characterized by the maculopapular rash typically beginning on the face at the hairline and then extending downward, becoming confluent (Figure 7). The convalescent phase begins when the rash begins to disappear as do all the other symptoms. The rash may be minimal in children with measles modified by previous vaccine administration. Complications of measles include pneumonia, otitis media, myocarditis, pericarditis, and encephalitis.[104]

2.3.2 | Neurologic complications of measles

There are four main types of neurologic complications with measles.[105] Early in infection, acute encephalitis may occur in as many as 1:1000 infected people.[106] Approximately 2 weeks after the rash appears, acute demyelinating encephalomyelitis (ADEM) may appear. It is an autoimmune phenomenon with no measles virus in the brain.[107] With a time frame of weeks to months after infection, measles inclusion body encephalitis (MIBE) can occur, usually arising in immunocompromised patients. Finally, the fourth manifestation occurs several years after initial infection, subacute sclerosing panencephalitis (SSPE).

Acute encephalitis in measles occurs in approximately 1:1000 children.[106] The most typical age is 5–7 years and patients typically have the characteristic rash at the time of presentation.[108,109] Features include seizures, irritability and coma. Acute encephalitis is seen with increased frequency among those who are immunocompromised and in particular those with innate defects of host defense.[110–112] In a murine model, T-cell deficiency was associated with greater neurologic disease in adult mice.[113] However, in an outbreak of measles in South Africa in 2009–2010, MIBE was observed but not acute encephalitis nor ADEM.[114]

MIBE is known to occur almost exclusively in people with immune compromise. Disease features often include a milder rash than

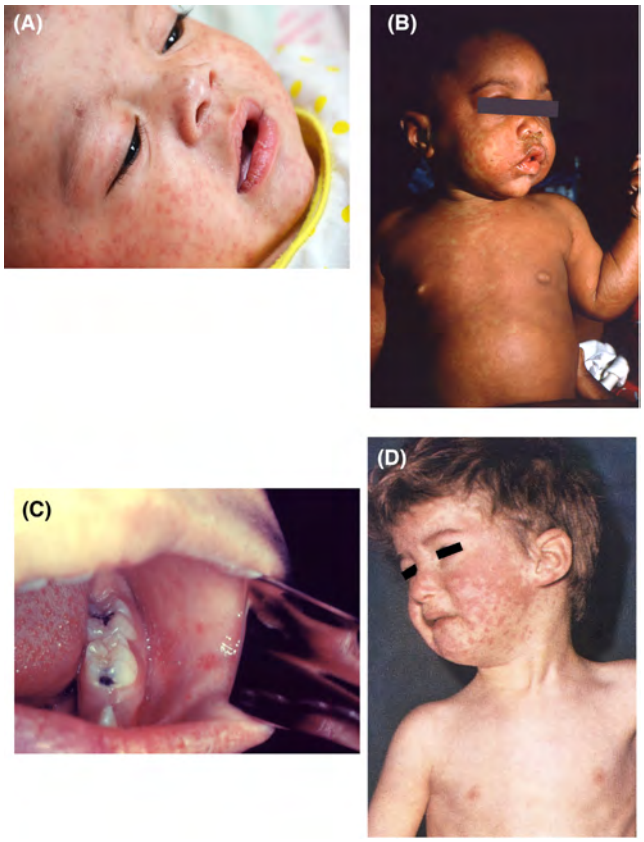


FIGURE 7 Features of measles. (A,B,D) measles rash. The rash typically begins on the face as in panels (A) and (D) and spreads distally (B). Koplik spots are shown in panel (C). All photos are from the CDC public health photo library.

is typical due to the immunocompromise. Seizures are the hallmark of this complication and sympathetic dysfunction is relatively common. The most common trajectory is progressive disease and death. Pathologic examination demonstrates inclusion bodies in neurons and glial cells[115] but inflammation is limited. The CSF is often bland but can have mildly increased protein and a few cells. CSF antibody titers will rise over time. The diagnosis is usually established through PCR detection of measles in CSF or brain tissue. The measles virus has been reported to have similar patterns of mutations in N and F genes to those recovered in SSPE although this was not seen in the outbreak in South Africa.[114] Some F gene mutations lead to a hyperfusogenic virus, allowing it to enter the CD150 negative neuronal cells.[116] M protein mutations are almost invariably found, leading to compromise in measles particle formation, thought to facilitate immune evasion.[117,118]

SSPE is a feared but thankfully rare complication of measles with 5–10 cases per 100,000 cases of measles although there is remarkable geographic heterogeneity.[119] Compromised clearance of the measles virus may contribute to the susceptibility to SSPE as the incidence appears to be higher in HIV and with earlier onset. Acquired variants in M and F proteins, as described above, lead to viral features contributing to neuroinvasion and viral persistence.[120] Patients present 5–10 years after acute infections with cognitive impairment and then develop myoclonic seizures evolving to become nearly continuous.[121] An infrequent but key sign is necrotizing retinitis. SSPE is pathologically characterized by neuronophagia, microglial nodules, and intranuclear inclusions in neurons and oligodendroglial cells. Neurofibrillary tangles are seen in later stages of the illness.[120] On imaging, demyelination can be observed usually starting in the temporal and parietal lobes with hyperintensities in the periventricular region. Late in the course, diffuse atrophy dominates the images.[121] The rarity of SSPE makes it difficult to generalize about the risks related to immune compromise. Several studies have identified changes to T-cell behavior in SSPE, but it remains unclear whether this is secondary to the disease process or causal. Small studies suggest an increased risk and earlier onset in children with HIV infected with measles.[120,122,123] However, a key mechanism of disease appears to be virus intrinsic. Acquired mutations leading to altered activity of the F protein and M protein appear to be in part responsible for SSPE. SSPE is characterized by high titer antibody to measles in the CSF, oligoclonal bands, and an increased CSF IgG index. Diagnostic criteria have been published and direct detection of the measles virus is not required and it is important to recognize that the acquired mutations may make it difficult or impossible to detect viral nucleic acids.[124]

2.3.3 | Measles in IEI

Risk factors for severe disease include immunocompromise, malnutrition, and pregnancy. HIV is the most common immune deficiency worldwide and provides most of the literature on measles in the setting of immune compromise. In HIV, pneumonia is the most common complication with acute kidney injury and encephalitis also being more common in those with HIV.[125]

MIBE is more common in people who are immunocompromised and some would say that MIBE is a sign of immune compromise.[126] There are multiple reports of patients with leukemia or HIV developing MIBE.[115,127,128] Cases after hematopoietic cell transplantation have been described as well.[129] Prior to the current availability of genetic testing for IEI, dysgammaglobulinemia and CID were common descriptors for some patients who developed disseminated measles.[112,130,131] Some of these patients had encephalitis from natural infection and a few had encephalitis from the measles vaccine. A theme among these cases is T-cell compromise.

In the modern era of newborn screening for SCID and population vaccination, patients with vaccine-derived disseminated measles and acute encephalitis have more frequently had defects of the innate immune system, usually the Type I interferon pathway. Complete *STAT1*, *STAT2*, and *IFNAR2* deficiencies (but not *IRF7* nor *IRF9* deficiencies) were found to have disseminated measles with vaccine strain measles virus,[111,132–134] often including acute encephalitis. These patients had a high fatality rate.

2.3.4 | Diagnosis

In the acute dissemination phenotype, PCR will usually detect the virus in CSF, blood, or nasopharyngeal swab. With measles pneumonitis, virus is usually easily detected by PCR from a lavage sample.

MIBE, in contrast, can be difficult to diagnose. The characteristic measles rash is not always present and the focal seizures are not pathognomonic. The seizures may be hard to control and the EEG may show epilepsia partialis continua but the seizure spectrum is large and not always specifically suggestive of MIBE. CSF antibodies to measles are usually undetectable initially and imaging can be normal early in the process. Diagnosis requires brain biopsy and glial cell proliferation with focal necrosis is typical but not diagnostic. Inclusion bodies are present by light microscopy, and electron microscopic studies demonstrate characteristic tubular structures consistent with the paramyxovirus nucleocapsid which are strongly suggestive of MIBE. RT-PCR for measles virus or immunohistochemistry will usually firmly establish the diagnosis.

SSPE is particularly difficult to diagnose in areas with little circulating measles due to its rarity, the delay in presentation from the acute measles infections, and the early manifestations having overlap with other neurologic conditions. The early features are irritability, psychiatric symptoms, and developmental regression. In adults, it can be mistaken for dementia. Later, the characteristic myoclonus develops. There may be associated dystonia and other neurologic findings. A subset of patients have early retinal changes that can be a useful diagnostic clue. The diagnostic gold standard is brain biopsy, and in regions with little measles exposure is probably the usual approach. The biopsy shows inflammation of meninges and cortex, necrosis, demyelination, and viral inclusion bodies. Measles virus may or may not be detectable by PCR from brain tissue and PCR detection can occur in seemingly normal individuals.[135] There are clinical criteria that have been put forward as an alternative and are often used when brain biopsy is not feasible or in resource constrained settings.[124] EEG high-amplitude slow waves occurring bilaterally and synchronously are seen in approximately75% of patients and are a useful diagnostic clue.

2.3.5 | Management

There are no agents with demonstrated efficacy for any of the forms of measles infection. Ribavirin has been used with some success to treat measles infections.[136,137] Specifically for MIBE, ribavirin has been used with about a quarter of the patients showing improvement.[127,129,130] Interferon-α has been used with similar limited efficacy.[138,139] Treatment for SSPE has recently been reviewed.[140] Individual agents showed poor efficacy, however, greater success was seen with combined interferon-α, inosine pranobex, and lamivudine[141] where >80% survival was seen.

2.4 | Papillomavirus

2.4.1 | Viral characteristics

Over 200 papillomaviruses have been identified and completely sequenced, including more than 150 human papillomaviruses (HPV). The viruses are non-enveloped icosahedral structures with double-stranded DNA circles encoding 8–9 genes. The number of encoded proteins is much greater, due to multiple promoters and splicing events.

HPVs are commonly isolated from skin swabs and hair follicles from normal immunocompetent individuals in the general population leading to the concept that they generally act as commensals.[142] HPV are divided into five genera by sequence and each genus has multiple types (and species) that are often categorized as high risk, meaning oncogenic, or low risk. Specific HPV types also exhibit tissue tropism, that is, skin or mucosa, with some viral types having dual tropism. Beta and gamma HPV types are largely commensals. The alpha, mu and nu HPV can cause visible papillomas with alpha HPV being by far the most common in the general population. The oncogenic properties will be covered below but a subgroup of 12 mucosal alpha HPV types are classified as high risk: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV16 is the most oncogenic of the HPVs. Eight other HPV types are classified as possibly carcinogenic: HPV26, 53, 66, 67, 68, 70, 73, and 8.[143,144] HPV6 and 11 are associated with benign genital warts, condylomata acuminata, and respiratory papillomatosis.[145,146] The HPV types causing common and plantar warts are largely comprised of HPV2, 3, 7, 10, 27, 28, and 57.

HPVs infect the basal epithelial cells through microlesions and replicate, leading to a stable level of 50–100 copies per cell in the basal layer with follicular stem cells possibly representing a reservoir.[147] The immune system is in large part responsible for elimination of HPV, even recognizing that many HPV establish a host-commensal relationship. Regression of anogenital warts is driven by host T-cell responses and people with medical immune suppression, HIV, or IEI affecting T cells are associated with increased spread and transformation to malignancy.[148–150] T-cell lymphopenia due to single ventricle physiology is associated relatively specifically with susceptibility to warts.[151]

2.4.2 | Phenotype of HPV in people with inborn errors of immunity

HPV infection in people with IEI includes benign warts, squamous cell carcinoma, or other HPV-driven malignancies.[152–155] Having an IEI alters the recovered HPV types, the extent of infection, and resistance to therapy.

A specific phenotype for HPV in people with IEI is epidermodysplasia verruciformis (EV).[156,157] It was known to be a genodermatosis long before any causal genes were recognized due to the

familial nature. Nevertheless, the definition rests on the virologic and pathologic features because it can also be seen with medical immunosuppression.[158] The clinical features include an eruption of pityriasis versicolor-like macules usually beginning in childhood and flat, wart-like papules, typically in sun-exposed areas.[159,160] Seborrheic keratosis-like plaques appear in adulthood with a predilection for sun-exposed areas. All the lesions have HPV. About 35%–50% of patients by middle age will have Bowen's-type carcinoma or invasive squamous cell carcinoma.[161] The HPV can be diverse but beta-HPVs 5 and 8 are the most commonly isolated.[162] Gamma-HPV are much less frequently seen in lesions. When EV occurs related to medical immunosuppression, the age of appearance relates to the age when the immunosuppression occurred.

A subset of EV has carried the descriptor "tree-man syndrome" due to the extensive horny skin growths often emanating from the hands. This colloquial term does a disservice to the patients. Two competing etiologies have been described. Autosomal recessive *CD28* deficiency was found in a single kindred with EV, one of whom could be classified as having extensive cutaneous horns.[158] *CD28* deficiency led to susceptibility to cutaneous alpha and gamma-HPVs, but the patient with extensive giant cutaneous horns had alpha-HPV2 recovered from the horny overgrowths while the other members of the kindred with EV had extensive warts with gamma-HPV4. The other etiology described for the condition of extensive giant horns related to HPV is a somatic variant in *ANKRD26*.[163] The single patient described had the characteristic cutaneous growths.

Extensive warts are common in many T-cell and NK cell disorders. Next-generation sequencing identified these IEI as having a strong phenotype of extensive beta-HPV: *CARMIL2*, *CD4*, *CORO1A*, *CXCR4*, *DCLRE1C*, *DOCK8*, *GATA2*, *IL7*, *LCK*, *MST1*, *RASGRP1*, *RHOH*, *TAOK2*, and *TPP2*. Of these conditions, *GATA2*, *DOCK8*, and *CXCR4* disorders represent the more common conditions associated with a strong predisposition to HPV. These T-cell disorders have susceptibility to other infections and malignancy risks and the HPV susceptibility is a component of overall viral susceptibility although warts may be the dominant virus in some conditions. Both cutaneous and mucosal disease occurs. A special subset of extensive warts can occur in patients with SCID due to mutations in *IL2RG* or *JAK3* post -hematopoietic cell transplant. The mechanism is incompletely understood but appears to be due to a keratinocyte specific defect.[164] The classic pure NK defects such as *MCM4*, *MCM10*, and *GINS1* deficiencies do not appear to have the same susceptibility to HPV as the T-cell defects.[165]

Isolated EV with no other clear viral susceptibility occurs in three recognized genetic conditions. *TMC6*, *TMC8*, and *CIB1* all encode proteins that complex to interact with HPV E5 and E8 proteins. These proteins restrict beta-HPV in the general population, where alpha, gamma and mu HPV are more common causes of warts. Mutation of one of genes encoding the complex proteins leads to beta-HPV susceptibility.[166] *TMC6*, *TMC8*, and *CIB1* deficiencies have the same phenotype of EV with no mucosal disease and can only be distinguished through sequencing or protein analysis.

2.4.3 | Management

For the T-cell intrinsic disorders, hematopoietic cell transplant usually leads to resolution of the warts. Often the conditioning leads to some improvement with sustained regression as engraftment occurs. For patients who cannot receive a transplant or who have ongoing graft dysfunction, various escalating treatments can be considered. There are no comparative trials but success has been seen with cryotherapy, laser treatment, and photodynamic therapy.[167] These physical approaches can work well but often the extensive nature of disease limits their use to small regions or problematic lesion clusters. Isotretinoin in combination with interferon-α has had some success.[168,169]

Plerixafor has been used specifically for CXCR4 disorders with success.[170] Topical cidofovir has been used successfully on sites less amenable to physical strategies.[171] Overall, the lesions in T-cell deficient individuals may be successfully cleared whereas in *TMC6*, *TMC8*, and *CIB1* deficiencies, the goal is to enhance function and minimize the risk of malignant transformation. Clearance is not possible at this time. In all cases, a critical component of management is sun restriction. For reasons incompletely understood, smoking and sun exposure both increase lesions and malignant transformation.

2.5 | Parvovirus B19

2.5.1 | Viral characteristics

Parvovirus B19 is a small non-enveloped single-stranded DNA virus of the family *Parvoviridae*, the subfamily *Parvovirinae*, and the genus *Erythrovirus*, meaning erythrocyte-infecting. Parvovirus B19 infects the erythroid progenitors in the bone marrow and triggers cell death either by lysis or by apoptosis through a mechanism driven by the nonstructural (NS)1 protein.[172] Parvovirus B19 infection causes a wide spectrum of clinical manifestations ranging from asymptomatic anemia to fatal aplastic crisis.[173] Rash, thrombocytopenia, leukopenia, miscarriage, hypocomplementemia, anemia, arthritis, and vasculitis are all recognized manifestations. By adulthood more than 70% of the adult population is seropositive to parvovirus B19 and most have had inconsequential infections. Approximately 25% of those infected are asymptomatic, 50% have systemic flu-like symptoms (myalgias, headache, and fever), and 25% have arthralgia or arthritis.[174] Parvovirus B19 is the only member of the family to cause clear-cut human disease although Parvovirus B4 has been identified in people with HIV and hepatitis C virus. It appears to be associated with more rapid progression of HIV[175] and two patients were identified with parvovirus B4 isolated from CSF in the setting of encephalitis.[176]

Parvovirus B19 is transmitted through respiratory secretions and blood products. It is one of the classic childhood exanthems, often going by "Fifth disease." In reality, most children do not display the classic features, however it is commonly conceptualized as

a triphasic illness. Early features are nonspecific viral symptoms of fever, malaise, myalgias, diarrhea, vomiting, and headache. The classic erythematous malar rash involving the cheeks ("slapped cheeks") with surrounding oral pallor develops as the fever resolves and lasts 4–5 days. A lacey reticular maculopapular rash develops on the trunk and limbs in some people around the time of resolution of the facial rash and lasts about 1 week.[174] Sun or heat may exacerbate the reticular rash.

2.5.2 | Anemia

Viremia occurs coincident with symptoms of fever and malaise. Erythroid progenitor cells become infected, then depleted, and the reticulocyte count drops. Anemia follows as the diminished reticulocytes cannot replete the circulating red cells and dying red cells. The reduction in the reticulocyte count is occasionally accompanied by leukopenia and thrombocytopenia.[177] Healthy people seldom notice the anemia, but severe anemia can occur in two specific settings. Patients with ongoing hemolysis due to autoantibodies or to an intrinsic erythrocyte disorder have an exaggerated nadir following infection. The second scenario is when the virus is not appropriately cleared. Patients with compromised immunity fail to clear the virus as quickly and so can have an exaggerated nadir. Aplastic anemia due to parvovirus B19 occurs after organ or bone marrow transplant and due to the poor antibody production (required for clearance), each episode can be severe. Generally, the aplastic crisis ends with the appearance of specific antibodies and thus rarely lasts for longer than 2 weeks but in severely immunocompromised patients, the aplastic phase can last much longer.

Most of the data on aplastic crises and persisting anemia in immunocompromised people has come from cohorts of patients with HIV. Nevertheless, IEI types with either T-cell defects, antibody deficiencies, or both have been described as associated with parvovirus B19-induced significant anemia. Given that antibody is felt to mediate clearance, it is to be expected that lymphoid disorders, as opposed to innate defects, would be the entities primarily associated with prolonged anemia or aplastic crisis. Case reports of patients having clinically significant infections with Nezelof syndrome, a T-cell disorder without a specific genetic etiology, common variable immunodeficiency, hyper IgM syndrome, and agammaglobulinema represent examples of lymphoid disorders.[178–181] These reports demonstrate the importance of adaptive control of parvovirus B19, nevertheless, given the high prevalence in communities, it is surprising that significant anemia is not reported more often in these vulnerable populations (Table 1).

2.5.3 | Arthritis

The study of parvovirus B19-induced arthritis and arthralgia has had a controversial arc with interpretations of data ranging from a clear causal relationship to pure epiphenomena. Acute parvovirus B19 infection can cause significant small joint edema, synovitis, and as can many infections, induction of rheumatoid factor. Arthritis is more common in adults (up to half of those with new infection) than children (5%–10%) and adults may be more likely to have a symmetric small joint polyarthritis.[182] The less clear aspect is whether it is a cause of rheumatoid arthritis. Most patients with acute parvovirus B19 arthritis will slowly resolve but still controversial is whether a subset evolve to rheumatoid arthritis driven by the viral infection. Complicating interpretation are a number of studies demonstrating parvovirus B19 DNA in joint aspirates from patients with rheumatoid arthritis.[183] The presence of DNA does not equate to causality, however. A key argument against the role of parvovirus is the distinct natural history. Rheumatoid arthritis (prebiologic era) was associated with progressive erosions while parvovirus B19 caused pain, edema, even synovitis, but did not cause erosions.

There have been a handful of case reports of parvovirus B19-associated arthritis in people who have IEI. These have generally been reported in people with agammaglobulinemia or CVID.[184]

2.5.4 | Encephalitis

Encephalitis occurs with parvovirus B19 and in one metagenomic survey of potentially infected patients found 2.2% ($N = 16$) had parvovirus B19 DNA detected. Of the nine patients who had parvovirus B19 DNA in CSF, none were immune compromised.[185] Nevertheless, parvovirus B19 encephalitis has been described in HIV suggesting that dissemination to the CNS may be controlled in part by host responses.[186,187] Arguing against this is the low numbers of clinically evident parvovirus B19 in Table 1. Overall, susceptibility to this virus does not appear to be dramatically, increased among patients with IEI.

2.5.5 | Hemophagocytic lymphohistiocytosis

There have been rare cases of HLH triggered by parvovirus B19, largely in the transplant literature. Small series of children with leukemia and parvovirus B19-induced HLH have also been reported.[188,189] Among patients with IEI, parvovirus B19 induced HLH has been reported in *ADA2* and *SH2D1A* disorders.[190,191]

Overall, susceptibility to this virus does not appear to be dramatically increased among patients with IEI with the possible exception of aplastic anemia related to delayed clearance of the virus.

2.5.6 | Diagnosis

Parvovirus B19 is almost universally detected by PCR in the clinical setting. Metagenomic sequencing has been useful in research settings.

2.5.7 | Management

Immunoglobulin has been used for significant anemia, with many recorded successes.[192–194] Its role in the treatment of myocarditis, arthritis, and encephalitis is less clear, but it is often used as a low-risk therapy in these circumstances.[195,196] Immunosuppression, often corticosteroids, has also been used.

2.6 | Summary of unusual viral phenotypes

Severe respiratory tract infections are dangerous for people living with IEI and their risks are understood. The unusual phenotypes described here are not the only viruses to cause harm in unusual ways in people with IEI. Herpes simplex encephalitis is another example. While seen in people believe to be immunocompetent, herpes simplex encephalitis is enriched in disorders affecting neuronal innate defenses and brain stem herpes simplex encephalitis is nearly only seen in two disorders of RNA metabolism.[197] Similarly, varicella encephalitis is enriched in people with disorders impacting DNA metabolism.[198] Thus, it is wise to keep an open mind regarding etiologies of unusual phenotypes. With the advent of metagenomic sequencing even more atypical viral infections have been found.[37,199]

3 | AUGMENTED INDUCTION OF MALIGNANCY

There are a number of examples of IEI in which malignancy risk is increased. Many of the T-cell disorders have an increased risk of lymphoma in part due to lack of control of Epstein–Barr virus.[200] There are also increased risks related to long-term use of medications, such as the increased risk of squamous cell carcinoma with prolonged use of voriconazole. The examples selected here include Merkel cell polyomavirus which is found only in those who are immune compromised. In contrast, papillomavirus and HSV do cause malignancy or growths in normal hosts but they are included in this section because there is a clear enrichment in IEI.

3.1 | Human Papillomavirus (HPV)

HPV types are broadly divided into low-risk HPV and high-risk HPV groups depending on their potential of malignant progression. Cervical cancer is the most extensively studied type of cancer induced by HPV, with 99% of cases being associated with high-risk HPV types. Nevertheless, cancers related to HPV also impact numerous other mucosal areas. Specifically in the general population, HPV infection is found in 70% of oropharyngeal cancers, 64%–91% of cervical/vaginal, 40%–50% of vulvar, 88%–94% of anal, and 40%–50% of penile cancers.[148,201] It is thought to represent a modest risk for skin cancer.[202]

Immunodeficiency and immune compromise are significant risk factors linked to malignant transformation with HPV.[200,203,204] Innate defects, T-cell defects, and NK cell defects are particularly associated with HPV susceptibility (see above). Uncontrolled HPV is the main driver of susceptibility to HPV-induced cancer although impaired surveillance of malignant cells may also be a contributor.[203] Key IEI impacting the adaptive immune system include *DOCK8* deficiency, WHIM syndrome due to *CXCR4* mutations, *GATA2* deficiency, and serine/threonine kinase 4 (*STK4*) deficiency. Cell intrinsic keratinocyte defects of host defense are also associated with a predisposition to HPV-induced malignancy.[205] These are comprised of the classic isolated EV: *TMC6*, *TMC8*, and *CIB1* deficiencies.

3.1.1 | Epidermodysplasia verruciformis

EV is characterized by the presence of widespread, persistent, flat warts, and macular lesions that typically appear during childhood, as described above. Classic verrucous warts are not common.[206] Squamous cell cancer (SCC) occurs in sun-exposed areas of the skin in 30%–70% of patients, typically by early adulthood.[156,168,207] The mechanism of HPV susceptibility was reviewed above but worth noting is a mild T-cell dysfunction.[208] This is not thought to be the major contributor to HPV but may contribute to the malignancy predisposition.

Beta HPV types, HPV5 and HPV8 most commonly, are found in lesions across the entire spectrum of early actinic lesions through late development of malignant transformation.[209] Beta-HPVs do not possess the E5 or E8 which are critical growth-promoting factors for keratinocytes in vivo.[209] Beta-HPVs attain pathogenicity only in genetically predisposed individuals[210] and in these conditions, the viral load is exceptionally high, implying lack of immune control.[211] HPV oncogenic genes are induced with sun exposure or wounding in mice and inhibition of E6 expression mitigates these physical traumas acting as inducers of oncogenesis.[212]

3.1.2 | WHIM syndrome (*CXCR4* disorder)

WHIM syndrome, a rare multisystem IEI characterized by warts, hypogammaglobulinemia, infections, and myelokathexis (retention of mature neutrophils in the bone marrow), is caused by autosomal dominant gain-of-function pathogenic variants in the *CXCR4* gene.[213] Patients with WHIM syndrome exhibit a remarkable susceptibility to HPV infection, leading to the discovery of numerous novel serotypes of the virus within this patient population.[214] Unlike patients with classic EV, patients with WHIM syndrome have predominantly gamma HPV recovered.[214] CXCR4 is a chemokine receptor that generally binds CXCL12, triggering activation of G proteins, cytoskeletal rearrangement, and anti-apoptotic signaling. Tonic activation results in desensitization of CXCR4, leukopenia, and altered myeloid and keratinocyte behavior.[215] Gain-of-function variants appear to stabilize the HPV oncogenic proteins E6 and E7, increase viral replication

in keratinocytes, leading to increased proliferation consistent with oncogenesis.[216]

Patients with WHIM syndrome have been reported to experience various HPV-related malignancies, including vulvar, cervical, and anorectal cancers, as well as precancerous genital lesions necessitating surgical management. Additionally, cases of HPV-related head and neck squamous cell carcinoma have been observed in these patients.[217,218] Inhibition of CXCR4 therapeutically improves warts as well as the leukopenia.[170]

3.1.3 | DOCK8 deficiency

Autosomal recessive loss-of-function mutations in *DOCK8* causes one of the more common combined immunodeficiencies.[219] DOCK8 deficiency is characterized by elevated serum IgE levels, chronic viral and fungal infections, food allergy, dermatitis, eosinophilia, decreased T and B cells, and an increased incidence of malignant tumors. HPV and herpes simplex viral infections represent common cutaneous viral infections in individuals with DOCK8 deficiency.[220]

Patients with DOCK8 deficiency are particularly susceptible to epithelial cancers.[221] About 40% of patients had warts and 39% had epithelial cancers. A multicenter study in Turkey revealed that DOCK8-deficient patients had the highest incidence of malignancy, with skin SCC and vulvar SCC being among the reported cancers. Insufficient immune responses leading to uncontrolled viral infections are believed to be the main factor driving malignancy in DOCK8 deficiency.[222] The eczema in DOCK8 deficiency can mask evolving SCC induced by HPV[223] and DOCK8-deficient patients developed mucocutaneous SCCs at a young age (range 16–25 years). Pediatricians are less familiar with SCC and the eczema may mask the evolution to SCC, therefore this complication is important to remember. The SCC arises in locations of chronic verrucae which can assist in the monitoring of patients for this high-risk complication.[224] The actinopathies, among which DOCK8 deficiency is a member, appear to have a higher rate of HPV and SCC than other similar T-cell disorders but the mechanism specific to the actinopathies is not fully understood.[225]

3.1.4 | GATA2 deficiency

Heterozygous pathogenic variants in the *GATA2* gene cause a highly variable disorder with incomplete penetrance.[226–229] GATA2 deficiency may present with infection such as *Mycobacterium avium* complex infection or cytopenias (dendritic cell, monocyte, B cell, and NK cells), syndromic features such as congenital deafness and lymphedema (originally defining Emberger syndrome), pulmonary or vascular involvement, and some patients present with myelodysplasia and/or acute myeloid leukemia (AML) and are identified through sequencing performed for those conditions.[230]

GATA2 haploinsufficiency is frequently associated with HPV infection (>50%).[227] GATA2 deficiency should be suspected in young women with severe cervical HPV disease. A study involving 35 females with GATA2 deficiency found that 27 of them were infected with HPV. Among these HPV-positive patients, 18 patients developed vulvar and/or cervical dysplasia. The median age of diagnosis for dysplasia was 27 years, ranging from 15 to 59 years. The median age of diagnosis for genital cancer in these patients was 34 years, ranging from 22 to 40 years.[230,231] Hematopoietic cell transplant is curative for HPV but not established SCC.[231]

3.1.5 | STK4 deficiency

Serine/threonine kinase 4 (*STK4*) deficiency (previously called MST1) is a relatively novel IEI in humans, with the first reported patients documented in 2012.[232] This autosomal recessive disorder is characterized by early-onset recurrent bacterial and viral infections, including lymphoproliferation and lymphoma induced by EBV.[233–235] Patients with *STK4* deficiency typically exhibit lymphopenia in CD4 T cells, CD8 T cells, and B cells. Many of these patients have also reported HPV-related warts.

STK4 is a tumor suppressor protein in immunocompetent individuals. However, in HPV-associated cervical cancer, STK4 levels are significantly reduced due to the suppression of STK4 mRNA by HPV E6 and E7 oncoproteins.[236] This facilitates HPV replication and tumor progression. Consequently, defects in STK4 increase HPV-driven oncogenesis in vitro.

Although there have been no reported cases of HPV-driven malignancy in STK4-deficient patients, the elevated risk of HPV-driven carcinogenesis and the presence of HPV-related cutaneous manifestations should be considered when caring for individuals with STK4 deficiency. STK4 is central to the etiopathogenesis of skin cancer.[237]

3.1.6 | Others

HPV induced dysplasia and/or cancer have been reported in several other IEI including *ICOS*, *SPINK5*, *ZAP70*, *RHOH*, *TPP2*, and *TAOK2* deficiencies as well as WILD syndrome and CADINS disease.[206,238,239]

3.1.7 | Diagnosis and management of HPV driven cancer in IEI

Biopsy and pathological diagnosis are the gold standard for malignancy. In terms of IEI diagnosis, any patient with extensive HPV disease or unusual HPV disease should have an immunologic evaluation including genetic sequencing.

HPV vaccination has demonstrated effectiveness in reducing HPV incidence among immunocompromised individuals. Nevertheless, further research is needed to determine the optimal dose frequency in immunocompromised hosts. Encouraging advancements are being made in the development of therapeutic vaccines, predominantly utilizing tumor proteins E6/E7 as the

foundation to trigger potent cellular immunity and potentially eliminate HPV-related diseases and malignancies.

Limiting sun exposure and regular screening of precancerous lesions remains the most effective method for detecting cancer and precancerous lesions, particularly in immunodeficient patients who require earlier and more frequent surveillance for HPV-related diseases.

The management of HPV-driven cancer incorporates surgery, chemotherapy, radiotherapy, and targeted immune therapy, with the treatment plan tailored to the location and stage of the cancer. Early nodal involvement usually necessitates surgical removal and radiation therapy, while more advanced tumors are treated with radiochemotherapy.

Patients with IEI may benefit from a distinct approach compared to the general population, as evidenced by the contrasting outcomes of radiotherapy for cutaneous SCC and EV. While radiotherapy effectively treats SCC in the general population, it can be counterproductive in individuals with EV, leading to the development of more aggressive tumors after treatment.[240,241] For GATA2 deficiency-related HPV disease, bone marrow transplantation represents the sole known curative treatment option.[231]

Adoptive cell transfer, genetically engineered T-cell therapy (involving T-cell receptors (TCRs) and chimeric antigen receptors (CARs)), and immune checkpoint inhibitors show promise but their role in IEI is unclear. New molecular technologies, such as zinc finger nucleases, CRISPR, and RNAi hold particular potential for effectively addressing severely immunocompromised patient populations.

3.2 | Merkel cell polyomavirus

Merkel cell polyomavirus (MCPyV) is a member of the Polyomaviridae family, characterized as a non-enveloped circular double-stranded DNA virus with a genome size of around 5.4 kb (kilobases). MCPyV infection is prevalent in the general population and is often asymptomatic.[242,243] Initial exposure to MCPyV commonly takes place during early childhood and the seroprevalence of the virus tends to rise among older age groups. Merkel cell carcinoma (MCC) is a rare yet aggressive form of skin cancer caused by MCPyV. In MCC, the primary lesion is a neuroendocrine tumor which typically presents as a solitary erythematous or violaceous papulonodule or plaque on sun-exposed skin, most commonly found on the head and neck, and sometimes on the extremities.[244] MCC can metastasize early without a recognizable primary tumor in about 4% of all cases.[245] The mortality rate of MCC is 33%, making it more lethal than other more prevalent skin cancer types.[246] MCC is associated with local recurrence, regional metastasis, and distant metastasis to the brain, bone, liver, lung, and heart in part explaining its lethality.[247] MCC is the second most common cause of skin cancer death after melanoma.[248]

In the United States, almost 80% of Merkel cell carcinoma (MCC) cases are associated with MCPyV, while the proportion is lower at around 25% in Australia.[249] The viral genome of MCPyV has also been detected in squamous cell cancer and cervical adenocarcinomas, as well as in lymphoid leukemias. However, it is important to note that there is currently no definitive evidence establishing the etiological link between MCPyV and malignancies other than MCC.

Excessive UV exposure, advanced age, and immunosuppression are significant risk factors contributing to the development of MCC. Organ transplantation, HIV, autoimmune diseases, and lymphoproliferative disorders are recognized risk factors.[250] MCPyV DNA becomes clonally integrated during oncogenesis and drives focal amplification of the DNA in a pattern similar to that observed for HPV integration sites.[251] Small T-antigen (T-Ag) and large T-Ag expression is critical. The small T-Ag plays a crucial role in promoting transcription and gene expression, inducing the transformation of fibroblasts, and is believed to initiate tumorigenesis. The large T-Ag increases mutagenesis via induction of APOBEC3B expression and inhibits the tumor suppressor genes retinoblastoma (Rb) and p53, causing uncontrolled proliferation of MCC cells.[252]

MCC is exceptionally uncommon among younger patients, as only 5% of cases manifest in individuals below the age of 50. A significant proportion of cases are linked to immunosuppression.[253] IEI associated with MCC include *GATA2* deficiency and other T-cell disorders.[254,255]

MCPyV positive MCC has been found in patients with EV and one study showed a strong association of EV-associated skin neoplasms with MCPyV which suggests a unique susceptibility to infections with MCPyV in these keratinocyte disorders.[256–258]

3.2.1 | Diagnosis

Diagnosing MCC depends on finding the characteristic features of neuroendocrine tumors on skin biopsy. The immunohistochemical marker cytokeratin-20 (CK20) is employed to differentiate MCC from other neuroendocrine carcinomas.[259] MCPyV is detected by sequencing or PCR.

3.2.2 | Management

For primary tumors lacking signs of metastases, the standard treatment involves complete surgical excision with appropriate surgical margins.[260] As occult metastasis in a lymph node is common, a sentinel lymph node biopsy is typically recommended. To enhance local tumor control, postoperative adjuvant radiotherapy is employed although checkpoint inhibitors have shown promise. Due to its high lethality, novel treatments are being explored, many of which are designed to augment immunity.[261] Monitoring is a component of all treatment regimens as recurrence risks are high. Antibodies to MCPyV oncoproteins can be tracked as surveillance for recurrence,[261] however, immune compromise is a common predisposition

to MCC which may impact antibody production. IEI and all forms of immune compromise require more thoughtful and frequent monitoring.[262]

3.3 | Herpes simplex virus

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are human viruses with linear double-stranded DNA genomes, and they are categorized within the *Alphaherpesvirinae* subfamily. HSVs can enter a latent state within neurons, occasionally reactivating. HSV can be shed from mucous membranes, even without visible ulcers but active disease exhibits clusters of painful blisters on an erythematous background at the infection site. Ulceration can occur as the vesicles break down. Primary HSV1 infections, often in children, can also be associated with fever, intense pain, and lymphadenitis.[263] While HSV-1 is typically associated with orofacial lesions and HSV-2 with genital ulcers, the prevalence of genital herpes due to HSV-1 infection has markedly increased in recent years.[264] HSV infections are generally unpleasant but benign;however, they can result in severe clinical outcomes such as permanent loss of vision, encephalitis, meningitis, and even fatality, despite treatment with antivirals.[265–267]

3.3.1 | IEIs with susceptibility to HSV infections

Numerous inborn errors of immunity (IEIs) frequently manifest as severe or recurrent mucocutaneous lesions triggered by HSV. NK and/or T-cell defects are most often associated with mucosal HSV infections while some innate disorders are associated with herpes simplex encephalitis.[197,268–271]

3.3.2 | HSV and malignancy

The connection between HSV-1/HSV-2 and cancer has long been a subject of controversy. Despite not being standalone oncogenic viruses, HSV-1 has been identified in both benign and malignant thyroid tumors, prostate cancer, cervical cancer, and melanoma.[272] Several studies have detected HSV-1 within cancerous tissues and demonstrated its ability to disrupt cellular DNA damage repair and amplify preexisting oncogenes.[273] HSV-1 has been proposed as a co-carcinogen in oral squamous cell carcinoma, potentially collaborating with other carcinogens to enhance their tumorigenic effects.

3.3.3 | Tumor-like presentations of HSV

Hypertrophic herpes simplex genitalis (HHSG)

HHSG stands as a rare anogenital manifestation of herpes simplex virus (HSV) infection, often observed among immunocompromised patients, particularly those with HIV.[274] These painful nodular lesions can become malignant. On pathology, glassy intranuclear inclusions are indicative of HSV-1 or HSV-2.[274]

Herpes vegetans

Herpes vegetans is an uncommon and atypical form of cutaneous HSV infection, primarily documented among individuals with HIV.[275] These growths can be misidentified as malignancies. This complication has also been documented in various IEIs.[270,276] In immunodeficient patients with rapidly growing cutaneous masses, herpes simplex vegetans should be included in the differential diagnoses.

3.3.4 | Management

Acyclovir or related agents have been useful in patients with IEI.[277] Foscarnet was used successfully in a patient with *NFKB2* deficiency.[270] Subcutaneous pegylated interferon-α 2b has been used in recalcitrant cases, starting at a dose of 0.6 μg/kg/week, followed by 1 μg/kg/week.[277]

3.4 | Conclusions

HPV-induced SCC is the best known augmented cutaneous malignancy in people with IEI. Frustratingly, current therapeutics are unsatisfactory for the most severe cases with classic EV. The use of topical cidofovir has improved outcomes for the people with T-cell disorders[171] although many cases respond to early topical approaches used in the general population. The tumors associated with HSV are not true malignancies but represent benign growths that are problematic and similar to HPV, can cause local destruction or dysfunction. There are two other tumors associated with IEI that bear mention. EBV smooth muscle tumors are a unique manifestation of EBV thus far only seen in certain IEI. Patients with *GATA2*, *CARMIL2*, and hypomorphic SCID have been described along with a poorly understood NK disorder.[278] Thus far, all conditions reported with an EBV smooth muscle tumor have had significant T-cell or NK cell dysfunction, similar to the overall susceptibility pattern to all EBV morbidities.

Kaposi sarcoma was found in a similarly restricted set of disorders. Human herpesvirus 8 (HHV-8) is found in all forms of Kaposi sarcoma: classical, endemic, AIDS-associated, and iatrogenically acquired. HHV-8 has been detected in tissues from Kaposi sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Among all these HHV-8 associated disorders, only Kaposi sarcoma and multicentric Castelman's disease are strongly associated with immune compromise. Classically seen in HIV, Kaposi sarcoma has been observed in IEI including Wiskott–Aldrich syndrome, *MAGT1* deficiency, *STIM1* deficiency, and other significant T-cell disorders, which conceptually aligns with HIV pathogenesis.[279]

In a USIDNET study, lymphoid cancers were the most frequently identified in patients with IEI with skin cancer as the second most

commonly identified malignancy.[200] Gastrointestinal cancers ranked third. When assessing the frequency of malignancy in IEI compared to the general population, lymphoid cancer, skin cancer, stomach cancer, and thyroid cancer were all enriched in the IEI cohort. The role of infection, that is, EBV, *Helicobacter pylori*, HPV, and unknown agents play an as yet incompletely understood role. An improved understanding may translate to improved therapeutics for patients with IEI.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2022;42(7):1473-1507.
2. Duncan CJA, Randall RE, Hambleton S. Genetic lesions of type I interferon signalling in human antiviral immunity. *Trends Genet*. 2021;37(1):46-58.
3. Abolhassani H, Delavari S, Landegren N, et al. Genetic and immunologic evaluation of children with inborn errors of immunity and severe or critical COVID-19. *J Allergy Clin Immunol*. 2022;150(5):1059-1073.
4. Matuozzo D, Talouarn E, Marchal A, et al. Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19. *medRxiv*. 2022.
5. Zhang Q, Matuozzo D, Le Pen J, et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *J Exp Med*. 2022;219(8):e20220131.
6. Otto WR, Behrens EM, Teachey DT, et al. Human adenovirus 7-associated hemophagocytic lymphohistiocytosis-like illness: clinical and virological characteristics in a cluster of five pediatric cases. *Clin Infect Dis*. 2021;73(7):e1532-e1538.
7. Si SJ, Tasian SK, Bassiri H, et al. Diagnostic challenges in pediatric hemophagocytic lymphohistiocytosis. *J Clin Immunol*. 2021;41(6):1213-1218.
8. Bode SF, Ammann S, Al-Herz W, et al. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. *Haematologica*. 2015;100(7):978-988.
9. Chinn IK, Eckstein OS, Peckham-Gregory EC, et al. Genetic and mechanistic diversity in pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2018;132(1):89-100.
10. Birndt S, Schenk T, Heinevetter B, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. *J Cancer Res Clin Oncol*. 2020;146(4):1065-1077.
11. Meeths M, Bryceson YT. Genetics and pathophysiology of haemophagocytic lymphohistiocytosis. *Acta Paediatr*. 2021;110(11):2903-2911.
12. Tangye SG, Palendira U, Edwards ES. Human immunity against EBV-lessons from the clinic. *J Exp Med*. 2017;214(2):269-283.
13. Sullivan KE, Puck JM, Notarangelo LD, et al. USIDNET: a strategy to build a community of clinical immunologists. *J Clin Immunol*. 2014;34(4):428-435.
14. Adams MJ, Carstens EB. Ratification vote on taxonomic proposals to the international committee on taxonomy of viruses (2012). *Arch Virol*. 2012;157(7):1411-1422.
15. Simmonds P, Gorbalenya AE, Harvala H, et al. Recommendations for the nomenclature of enteroviruses and rhinoviruses. *Arch Virol*. 2020;165(3):793-797.
16. CDC. *Non-polio enterovirus*. 2015 http://www.cdc.gov/non-polio-enterovirus/about/overview.html
17. Khetsuriani N, Lamonte A, Oberste MS, Pallansch M. Neonatal enterovirus infections reported to the national enterovirus surveillance system in the United States, 1983–2003. *Pediatr Infect Dis J*. 2006;25(10):889-893.
18. Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med*. 1993;86(1):31-42.
19. Halliday E, Winkelstein J, Webster A. Enteroviral infections in primary immunodeficiency (PID): a survey of morbidity and mortality. *J Infect*. 2003;46(1):1-8.
20. Wilfert CM, Buckley RH, Mohanakumar T, et al. Persistent and fatal central-nervous-system ECHOvirus infections in patients with agammaglobulinemia. *N Engl J Med*. 1977;296(26):1485-1489.
21. Bardelas JA, Winkelstein JA, Seto DS, Tsai T, Rogol AD. Fatal ECHO 24 infection in a patient with hypogammaglobulinemia: relationship to dermatomyositis-like syndrome. *J Pediatr*. 1977;90(3):396-399.
22. Scaravilli F, Coutinho P. Lymphocytic encephalitis in a case of agammaglobulinaemia. *Acta Neuropathol*. 1973;25(3):188-195.
23. O'Toole D, Groth D, Wright H, et al. X-linked agammaglobulinemia: infection frequency and infection-related mortality in the USIDNET registry. *J Clin Immunol*. 2022;42(4):827-836.
24. Hernandez-Trujillo V, Zhou C, Scalchunes C, et al. A registry study of 240 patients with X-linked agammaglobulinemia living in the USA. *J Clin Immunol*. 2023;43(6):1468-1477.
25. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr*. 1999;134(5):589-596.
26. McKinney RJ, Katz S, Wilfert C. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. *Rev Infect Dis*. 1987;9(2):334-356.
27. Rudge P, Webster A, Revesz T, et al. Encephalomyelitis in primary hypogammaglobulinaemia. *Brain*. 1996;119(Pt 1):1-15.
28. Ito N, Kokubo Y, Narita Y, Naito Y, Kuzuhara S. A case of agammaglobulinemia with chronic enteroviral meningomyelitis. *Rinsho Shinkeigaku*. 1996;36(2):306-311.
29. Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-linked agammaglobulinemia:

update on epidemiology and therapy. *J Allergy Clin Immunol Pract*. 2016;4(6):1059-1065.
30. Ozdoba C, Ramelli G, Schroth G. MRI in a patient with congenital agammaglobulinaemia. *Neuroradiology*. 1998;40(8):516-518.
31. Sole D, Radvani J, Leser P, Naspitz C. Magnetic resonance imaging in a patient with X-linked agammaglobulinemia and chronic meningoencephalitis. *J Investig Allergol Clin Immunol*. 1992;2(1):43-45.
32. Lerner E, Bilaniuk L. Bruton-type (congenital X-linked) agammaglobulinemia: MR imaging of unusual intracranial complications. *AJNR Am J Neuroradiol*. 1992;13(3):976-980.
33. Ozawa T, Onodera O, Iizuka O, et al. A case of chronic enteroviral meningitis and hydrocephalus associated with Bruton type agammaglobulinemia. *No to Shinkei*. 1998;50(2):191-196.
34. Shaker O, Abdelhamid N. Detection of enteroviruses in pediatric patients with aseptic meningitis. *Clin Neurol Neurosurg*. 2015;129:67-71.
35. Hyeon J, Hwang S, Kim H, et al. Accuracy of diagnostic methods and surveillance sensitivity for human enterovirus, South Korea, 1999–2011. *Emerg Infect Dis*. 2013;19(8):1268-1275.
36. Wilfert CM, Lehrman SN, Katz SL. Enteroviruses and meningitis. *Pediatr Infect Dis*. 1983;2(4):333-341.
37. Quan PL, Wagner TA, Briese T, et al. Astrovirus encephalitis in boy with X-linked agammaglobulinemia. *Emerg Infect Dis*. 2010;16(6):918-925.
38. Ziegner UH, Kobayashi RH, Cunningham-Rundles C, et al. Progressive neurodegeneration in patients with primary immunodeficiency disease on IVIG treatment. *Clin Immunol*. 2002;102(1):19-24.
39. Jyonouchi S, Jongco AM, Puck J, Sullivan KE. Immunodeficiencies associated with abnormal newborn screening for T cell and B cell lymphopenia. *J Clin Immunol*. 2017;37(4):363-374.
40. Boyarchuk O, Yarema N, Kravets V, et al. Newborn screening for severe combined immunodeficiency: the results of the first pilot TREC and KREC study in Ukraine with involving of 10,350 neonates. *Front Immunol*. 2022;13:999664.
41. Ahmed R, Buckland M, Davies L, et al. Enterovirus 71 meningoencephalitis complicating rituximab therapy. *J Neurol Sci*. 2011;305(1–2):149-151.
42. Anderson SM, Gold D, Olson G, Pisano J. Chronic aseptic meningitis caused by enterovirus in a humorally immunosuppressed adult patient presenting with sensorineural hearing loss: a case report. *BMC Infect Dis*. 2022;22(1):16.
43. Archimbaud C, Bailly JL, Chambon M, Tournilhac O, Travade P, Peigue-Lafeuille H. Molecular evidence of persistent echovirus 13 meningoencephalitis in a patient with relapsed lymphoma after an outbreak of meningitis in 2000. *J Clin Microbiol*. 2003;41(10):4605-4610.
44. Cameron Smail R, O'Neill JH, Andresen D. Brainstem encephalitis caused by Coxsackie A16 virus in a rituximab-immunosuppressed patient. *BMJ Case Rep*. 2019;12(8):e230177.
45. Cheema S, Bunting E, Good C, Hajela V, Ridha BH, Saha RA. Balancing immunosuppression and infection: recurrent enterovirus encephalitis in SLE. *Pract Neurol*. 2019;19(6):508-510.
46. Cook SG, Ford AW, Lindholm DA, Scott J. Enteroviral meningoencephalitis as a complication of rituximab therapy for rheumatoid arthritis. *Cureus*. 2021;13(9):e18189.
47. Epstein S, Thakkar R, Fong KT, et al. Compassionate-use pocapavir and immunoglobulin therapy for treatment of rituximab-associated enterovirus meningoencephalitis. *J Neurovirol*. 2022;28(2):329-334.
48. Heger JM, Eichenauer DA, Kasper P, Boll B, Shimabukuro-Vornhagen A, Kochanek M. Fatal disseminated enterovirus infection in a patient with follicular lymphoma undergoing obinutuzumab maintenance therapy. *Eur J Haematol*. 2019;103(3):268-271.
49. Kapadia RK, Gill CM, Baca C, et al. Enterovirus A71 causing meningoencephalitis and acute flaccid myelitis in a patient receiving rituximab. *J Neuroimmunol*. 2021;358:577639.
50. Luciani L, Ninove L, Zandotti C, et al. Fatal underhanded chronic enterovirus infection associated with anti-CD20 monotherapy for central nervous system demyelinating disease. *Mult Scler*. 2021;27(2):320-323.
51. Sellier-Leclerc AL, Belli E, Guerin V, Dorfmuller P, Deschenes G. Fulminant viral myocarditis after rituximab therapy in pediatric nephrotic syndrome. *Pediatr Nephrol*. 2013;28(9):1875-1879.
52. Shaheen N, Mussai F. Enteroviral encephalitis in a child with CNS relapse of Burkitt leukemia treated with rituximab. *J Pediatr Hematol Oncol*. 2019;41(1):e27-e29.
53. Tekin B, Boire N, Shah K, Hanson J, Bridges AG. Viral panniculitis in a patient with disseminated opportunistic enterovirus infection. *J Cutan Pathol*. 2021;48(3):434-438.
54. Vermeersch G, Laenen L, Lens G, et al. Antiviral treatment with fluoxetine for rituximab-associated chronic echovirus 13 meningoencephalitis and myofasciitis. *Eur J Neurol*. 2022;29(10):3117-3123.
55. Higer M, Cana D, Podlech J, et al. Life-threatening disseminated enterovirus infection during combined rituximab and ibrutinib maintenance treatment for mantle cell lymphoma: a case report. *J Med Case Reports*. 2020;14(1):135.
56. Grisariu S, Vaxman I, Gatt M, et al. Enteroviral infection in patients treated with rituximab for non-Hodgkin lymphoma: a case series and review of the literature. *Hematol Oncol*. 2017;35(4):591-598.
57. El-Sayed ZA, Abramova I, Aldave JC, et al. X-linked agammaglobulinemia (XLA): phenotype, diagnosis, and therapeutic challenges around the world. *World Allergy Organ J*. 2019;12(3):100018.
58. Misbah S, Spickett G, Ryba P, et al. Chronic enteroviral meningoencephalitis in agammaglobulinemia: case report and literature review. *J Clin Immunol*. 1992;12(4):266-270.
59. Shiroma N, Omi T, Hasegawa H, Nagashima K, Ohta T. A case of X-linked agammaglobulinemia with progressive encephalitis. *Pediatr Neurol*. 2004;31(5):371-373.
60. von der Wense A, Herrmann B, Deppermann R, Harms F, Wehinger H. Intrathecal interferon therapy in chronic echovirus meningoencephalitis in Bruton type agammaglobulinemia. *Klin Padiatr*. 1998;210(2):51-55.
61. Dwyer J, Erlendsson K. Intraventricular gamma-globulin for the management of enterovirus encephalitis. *Pediatr Infect Dis J*. 1988;7(5 Suppl):S30-S33.
62. Thibaut H, Leyssen P, Puerstinger G, Muigg A, Neyts J, De Palma A. Towards the design of combination therapy for the treatment of enterovirus infections. *Antiviral Res*. 2011;90(3):213-217.
63. Zhang G, Zhou F, Gu B, et al. In vitro and in vivo evaluation of ribavirin and pleconaril antiviral activity against enterovirus 71 infection. *Arch Virol*. 2012;157(4):669-679.
64. Rotbart H, Webster A. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis*. 2001;32(2):228-235.
65. Webster A. Pleconaril–an advance in the treatment of enteroviral infection in immuno-compromised patients. *J Clin Virol*. 2005;32(1):1-6.
66. Wildenbeest J, van den Broek P, Benschop K, et al. Pleconaril revisited: clinical course of chronic enteroviral meningoencephalitis after treatment correlates with in vitro susceptibility. *Antivir Ther*. 2012;17(3):459-466.
67. Thibaut H, De Palma A, Neyts J. Combating enterovirus replication: state-of-the-art on antiviral research. *Biochem Pharmacol*. 2012;83(2):185-192.
68. Collett MS, Neyts J, Modlin JF. A case for developing antiviral drugs against polio. *Antiviral Res*. 2008;79(3):179-187.
69. Oberste MS, Moore D, Anderson B, Pallansch MA, Pevear DC, Collett MS. In vitro antiviral activity of V-073 against polioviruses. *Antimicrob Agents Chemother*. 2009;53(10):4501-4503.

70. Model M, Collett S, Hinscks J, Oberste S. Anti-poliovirus activity of Pocapavir in a human mOPV1 challenge. Paper presented at: 15. Interscience Conference on Antimicrobial Agents and Chemotherapy 53rd Annual Meeting 2013; Denver, Colorado.
71. Ulferts R, van der Linden L, Thibaut H, et al. Selective serotonin reuptake inhibitor fluoxetine inhibits replication of human enteroviruses B and D by targeting viral protein 2C. *Antimicrob Agents Chemother*. 2013;57(4):1952-1956.
72. Zuo J, Quinn K, Kye S, Cooper P, Damoiseaux R, Krogstad P. Fluoxetine is a potent inhibitor of coxsackievirus replication. *Antimicrob Agents Chemother*. 2012;56(9):4838-4844.
73. Nishimura A, Uppuluri R, Raj R, et al. An international survey of allogeneic hematopoietic cell transplantation for X-linked Agammaglobulinemia. *J Clin Immunol*. 2023;in press.
74. Sun D, Heimall JR, Greenhawt MJ, Bunin NJ, Shaker MS, Romberg N. Cost utility of lifelong immunoglobulin replacement therapy vs hematopoietic stem cell transplant to treat agammaglobulinemia. *JAMA Pediatr*. 2022;176(2):176-184.
75. Cong H, Jiang Y, Tien P. Identification of the myelin oligodendrocyte glycoprotein as a cellular receptor for rubella virus. *J Virol*. 2011;85(21):11038-11047.
76. Winter AK, Moss WJ. Rubella. *Lancet*. 2022;399(10332):1336-1346.
77. Tingle AJ, Allen M, Petty RE, Kettyls GD, Chantler JK. Rubella-associated arthritis. I. Comparative study of joint manifestations associated with natural rubella infection and RA 27/3 rubella immunisation. *Ann Rheum Dis*. 1986;45(2):110-114.
78. Plotkin SA. Rubella eradication: not yet accomplished, but entirely feasible. *J Infect Dis*. 2021;224(12 Suppl 2):S360-S366.
79. Rabinowe SL, George KL, Loughlin R, Soeldner JS, Eisenbarth GS. Congenital rubella. Monoclonal antibody-defined T cell abnormalities in young adults. *Am J Med*. 1986;81(5):779-782.
80. Berry CL, Thompson EN. Clinico-pathological study of thymic dysplasia. *Arch Dis Child*. 1968;43(231):579-584.
81. Verder H, Dickmeiss E, Haahr S, et al. Late-onset rubella syndrome: coexistence of immune complex disease and defective cytotoxic effector cell function. *Clin Exp Immunol*. 1986;63(2):367-375.
82. Frey TK. Neurological aspects of rubella virus infection. *Intervirology*. 1997;40(2–3):167-175.
83. Townsend JJ, Baringer JR, Wolinsky JS, et al. Progressive rubella panencephalitis. Late onset after congenital rubella. *N Engl J Med*. 1975;292(19):990-993.
84. La Hey E, Baarsma GS, De Vries J, Kijlstra A. Clinical analysis of Fuchs' heterochromic cyclitis. *Doc Ophthalmol*. 1991;78(3–4):225-235.
85. Quentin CD, Reiber H. Fuchs heterochromic cyclitis: rubella virus antibodies and genome in aqueous humor. *Am J Ophthalmol*. 2004;138(1):46-54.
86. Ruokonen PC, Metzner S, Ucer A, Torun N, Hofmann J, Pleyer U. Intraocular antibody synthesis against rubella virus and other microorganisms in Fuchs' heterochromic cyclitis. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(4):565-571.
87. Knoll AB, Postole AS, Auffarth GU, Mackensen F. Frequency of dendritiform inflammatory cells in the cornea in herpetic anterior uveitis without clinical keratitis and Fuchs uveitis. *J Ophthalmic Inflamm Infect*. 2014;4:31.
88. Bodemer C, Sauvage V, Mahlaoui N, et al. Live rubella virus vaccine long-term persistence as an antigenic trigger of cutaneous granulomas in patients with primary immunodeficiency. *Clin Microbiol Infect*. 2014;20(10):O656-O663.
89. Zhang D, Wanat KA, Perelygina L, et al. Cutaneous granulomas associated with rubella virus: a clinical review. *J Am Acad Dermatol*. 2023;in press.
90. Buchbinder D, Hauck F, Albert MH, et al. Rubella virus-associated cutaneous granulomatous disease: a unique complication in immune-deficient patients, not limited to DNA repair disorders. *J Clin Immunol*. 2019;39(1):81-89.
91. Perelygina L, Plotkin S, Russo P, et al. Rubella persistence in epidermal keratinocytes and granuloma M2 macrophages in patients with primary immunodeficiencies. *J Allergy Clin Immunol*. 2016;138(5):1436-1439 e1411.
92. Perelygina L, Faisthalab R, Abernathy E, et al. Rubella virus infected macrophages and neutrophils define patterns of granulomatous inflammation in inborn and acquired errors of immunity. *Front Immunol*. 2021;12:796065.
93. Perelygina L, Chen MH, Suppiah S, et al. Infectious vaccine-derived rubella viruses emerge, persist, and evolve in cutaneous granulomas of children with primary immunodeficiencies. *PLoS Pathog*. 2019;15(10):e1008080.
94. Wanat KA, Perelygina L, Chen MH, et al. Association of persistent rubella virus with idiopathic skin granulomas in clinically immunocompetent adults. *JAMA Dermatol*. 2022;158:626.
95. Shields BE, Perelygina L, Samimi S, et al. Granulomatous dermatitis associated with rubella virus infection in an adult with immunodeficiency. *JAMA Dermatol*. 2021;157(7):842-847.
96. Zanella MC, Cordey S, Laubscher F, et al. Unmasking viral sequences by metagenomic next-generation sequencing in adult human blood samples during steroid-refractory/dependent graft-versus-host disease. *Microbiome*. 2021;9(1):28.
97. Perelygina L, Buchbinder D, Dorsey MJ, et al. Outcomes for Nitazoxanide treatment in a case series of patients with primary immunodeficiencies and rubella virus-associated granuloma. *J Clin Immunol*. 2019;39(1):112-117.
98. Perelygina L, Hautala T, Seppanen M, Adebayo A, Sullivan KE, Icenogle J. Inhibition of rubella virus replication by the broad-spectrum drug nitazoxanide in cell culture and in a patient with a primary immune deficiency. *Antiviral Res*. 2017;147:58-66.
99. Faisthalab R, Suppiah S, Dorsey M, Sullivan KE, Icenogle J, Perelygina L. Drug sensitivity of vaccine-derived rubella viruses and quasispecies evolution in granulomatous lesions of two ataxia-telangiectasia patients treated with Nitazoxanide. *Pathogens*. 2022;11(3):33.
100. Takeuchi K, Miyajima N, Nagata N, Takeda M, Tashiro M. Wild-type measles virus induces large syncytium formation in primary human small airway epithelial cells by a SLAM (CD150)-independent mechanism. *Virus Res*. 2003;94(1):11-16.
101. Hashimoto K, Ono N, Tatsuo H, et al. SLAM (CD150)-independent measles virus entry as revealed by recombinant virus expressing green fluorescent protein. *J Virol*. 2002;76(13):6743-6749.
102. Ohno S, Ono N, Seki F, et al. Measles virus infection of SLAM (CD150) knockin mice reproduces tropism and immunosuppression in human infection. *J Virol*. 2007;81(4):1650-1659.
103. Griffin DE. Measles immunity and immunosuppression. *Curr Opin Virol*. 2021;46:9-14.
104. Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis*. 2004;189(Suppl 1):S4-S16.
105. Patterson MC. Neurological complications of measles (Rubeola). *Curr Neurol Neurosci Rep*. 2020;20(2):2.
106. Diwan MN, Samad S, Mushtaq R, et al. Measles induced encephalitis: recent interventions to overcome the obstacles encountered in the management amidst the COVID-19 pandemic. *Diseases*. 2022;10(4):104.
107. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles virus infection: an hypothesis for altered immune responses. *J Infect Dis*. 1994;170(Suppl 1):S24-S31.
108. Fisher DL, Defres S, Solomon T. Measles-induced encephalitis. *QJM*. 2015;108(3):177-182.
109. Johnson RT, Griffin DE, Hirsch RL, et al. Measles encephalomyelitis–clinical and immunologic studies. *N Engl J Med*. 1984;310(3):137-141.
110. Hernandez N, Bucciol G, Moens L, et al. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. *J Exp Med*. 2019;216(9):2057-2070.

111. Duncan CJ, Mohamad SM, Young DF, et al. Human IFNAR2 deficiency: lessons for antiviral immunity. *Sci Transl Med*. 2015;7(307):307ra154.
112. Mawhinney H, Allen IV, Beare JM, et al. Dysgammaglobulinaemia complicated by disseminated measles. *Br Med J*. 1971;2(5758):380-381.
113. Lawrence DM, Vaughn MM, Belman AR, Cole JS, Rall GF. Immune response-mediated protection of adult but not neonatal mice from neuron-restricted measles virus infection and central nervous system disease. *J Virol*. 1999;73(3):1795-1801.
114. Hardie DR, Albertyn C, Heckmann JM, Smuts HE. Molecular characterisation of virus in the brains of patients with measles inclusion body encephalitis (MIBE). *Virol J*. 2013;10:283.
115. Albertyn C, van der Plas H, Hardie D, et al. Silent casualties from the measles outbreak in South Africa. *S Afr Med J*. 2011;101(5):313-314, 316–317.
116. Watanabe S, Ohno S, Shirogane Y, Suzuki SO, Koga R, Yanagi Y. Measles virus mutants possessing the fusion protein with enhanced fusion activity spread effectively in neuronal cells, but not in other cells, without causing strong cytopathology. *J Virol*. 2015;89(5):2710-2717.
117. Cattaneo R, Rebmann G, Baczko K, ter Meulen V, Billeter MA. Altered ratios of measles virus transcripts in diseased human brains. *Virology*. 1987;160(2):523-526.
118. Cattaneo R, Rebmann G, Schmid A, Baczko K, ter Meulen V, Billeter MA. Altered transcription of a defective measles virus genome derived from a diseased human brain. *EMBO J*. 1987;6(3):681-688.
119. Samia P, Oyieke K, Tunje D, et al. Options in the treatment of subacute sclerosing panencephalitis: implications for low resource areas. *Curr Treat Options Neurol*. 2022;24(3):99-110.
120. Mekki M, Eley B, Hardie D, Wilmshurst JM. Subacute sclerosing panencephalitis: clinical phenotype, epidemiology, and preventive interventions. *Dev Med Child Neurol*. 2019;61(10):1139-1144.
121. Jafri SK, Kumar R, Ibrahim SH. Subacute sclerosing panencephalitis—current perspectives. *Pediatric Health Med Ther*. 2018;9:67-71.
122. Manesh A, Moorthy M, Bandopadhyay R, Rupali P. HIV-associated sub-acute sclerosing panencephalitis—an emerging threat? *Int J STD AIDS*. 2017;28(9):937-939.
123. Kija E, Ndondo A, Spittal G, Hardie DR, Eley B, Wilmshurst JM. Subacute sclerosing panencephalitis in south African children following the measles outbreak between 2009 and 2011. *S Afr Med J*. 2015;105(9):713-718.
124. Dyken PR. Subacute sclerosing panencephalitis. Current status. *Neurol Clin*. 1985;3(1):179-196.
125. Diana NE, Feldman C. Measles in adults: a comparison of hospitalised HIV-infected and HIV-uninfected patients. *South Afr J HIV Med*. 2019;20(1):a877.
126. Jain R, Aulakh R. Measles-associated CNS complications: a review. *Journal of Child Science*. 2022;12:e172-e181.
127. Mustafa MM, Weitman SD, Winick NJ, Bellini WJ, Timmons CF, Siegel JD. Subacute measles encephalitis in the young immunocompromised host: report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. *Clin Infect Dis*. 1993;16(5):654-660.
128. Lievano F, Galea SA, Thornton M, et al. Measles, mumps, and rubella virus vaccine (M-M-RII): a review of 32 years of clinical and postmarketing experience. *Vaccine*. 2012;30(48):6918-6926.
129. Freeman AF, Jacobsohn DA, Shulman ST, et al. A new complication of stem cell transplantation: measles inclusion body encephalitis. *Pediatrics*. 2004;114(5):e657-e660.
130. Bitnun A, Shannon P, Durward A, et al. Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. *Clin Infect Dis*. 1999;29(4):855-861.
131. Monafo WJ, Haslam DB, Roberts RL, Zaki SR, Bellini WJ, Coffin CM. Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr*. 1994;124(2):273-276.
132. Burns C, Cheung A, Stark Z, et al. A novel presentation of homozygous loss-of-function STAT-1 mutation in an infant with hyperinflammation—a case report and review of the literature. *J Allergy Clin Immunol Pract*. 2016;4(4):777-779.
133. Hambleton S, Goodbourn S, Young DF, et al. STAT2 deficiency and susceptibility to viral illness in humans. *Proc Natl Acad Sci USA*. 2013;110(8):3053-3058.
134. Moens L, Van Eyck L, Jochmans D, et al. A novel kindred with inherited STAT2 deficiency and severe viral illness. *J Allergy Clin Immunol*. 2017;139(6):1995-1997 e1999.
135. Katayama Y, Hotta H, Nishimura A, Tatsuno Y, Homma M. Detection of measles virus nucleoprotein mRNA in autopsied brain tissues. *J Gen Virol*. 1995;76(Pt 12):3201-3204.
136. Shigeta S, Mori S, Baba M, et al. Antiviral activities of ribavirin, 5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide, and 6′-(R)-6′-C-methylneplanocin A against several ortho- and paramyxoviruses. *Antimicrob Agents Chemother*. 1992;36(2):435-439.
137. Uylangco CV, Beroy GJ, Santiago LT, Mercoleza VD, Mendoza SL. A double-blind, placebo-controlled evaluation of ribavirin in the treatment of acute measles. *Clin Ther*. 1981;3(5):389-396.
138. Olding-Stenkvist E, Forsgren M, Henley D, et al. Measles encephalopathy during immunosuppression: failure of interferon treatment. *Scand J Infect Dis*. 1982;14(1):1-4.
139. Simpson R, Eden OB. Possible interferon response in a child with measles encephalitis during immunosuppression. *Scand J Infect Dis*. 1984;16(3):315-319.
140. Pritha A, Medha T, Garg R. A comprehensive investigation of the current subacute sclerosing panencephalitis (SSPE) treatment options to improve patient quality of life. *Cureus*. 2022;14:e228389.
141. Aydin OF, Senbil N, Kuyucu N, Gurer YK. Combined treatment with subcutaneous interferon-alpha, oral isoprinosine, and lamivudine for subacute sclerosing panencephalitis. *J Child Neurol*. 2003;18(2):104-108.
142. Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. *J Virol*. 2000;74(24):11636-11641.
143. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens–part B: biological agents. *Lancet Oncol*. 2009;10(4):321-322.
144. Halec G, Schmitt M, Dondog B, et al. Biological activity of probable/possible high-risk human papillomavirus types in cervical cancer. *Int J Cancer*. 2013;132(1):63-71.
145. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope*. 2008;118(7):1236-1247.
146. Ball SL, Winder DM, Vaughan K, et al. Analyses of human papillomavirus genotypes and viral loads in anogenital warts. *J Med Virol*. 2011;83(8):1345-1350.
147. Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. *Viruses*. 2015;7(7):3863-3890.
148. Shamanin V, zur Hausen H, Lavergne D, et al. Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. *J Natl Cancer Inst*. 1996;88(12):802-811.
149. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis*. 1995;171(4):1026-1030.
150. Brickman C, Palefsky JM. Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era. *Curr HIV/AIDS Rep*. 2015;12(1):6-15.
151. Morsheimer MM, Rychik J, Forbes L, et al. Risk factors and clinical significance of lymphopenia in survivors of the Fontan procedure for single-ventricle congenital cardiac disease. *J Allergy Clin Immunol Pract*. 2016;4(3):491-496.

152. Leiding JW, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol*. 2012;130(5):1030-1048.
153. Beziat V. Human genetic dissection of papillomavirus-driven diseases: new insight into their pathogenesis. *Hum Genet*. 2020;139(6–7):919-939.
154. Ruffner MA, Sullivan KE, Henrickson SE. Recurrent and sustained viral infections in primary immunodeficiencies. *Front Immunol*. 2017;8:665.
155. Hewavisenti RV, Arena J, Ahlenstiel CL, Sasson SC. Human papillomavirus in the setting of immunodeficiency: pathogenesis and the emergence of next-generation therapies to reduce the high associated cancer risk. *Front Immunol*. 2023;14:1112513.
156. Lutzner MA, Blanchet-Bardon C, Orth G. Clinical observations, virologic studies, and treatment trials in patients with epidermodysplasia verruciformis, a disease induced by specific human papillomaviruses. *J Invest Dermatol*. 1984;83(1 Suppl):18s-25s.
157. Androphy EJ, Dvoretzky I, Lowy DR. X-linked inheritance of epidermodysplasia verruciformis. Genetic and virologic studies of a kindred. *Arch Dermatol*. 1985;121(7):864-868.
158. Uitto J, Saeidian AH, Youssefian L, et al. Recalcitrant warts, epidermodysplasia verruciformis, and the tree-man syndrome: phenotypic spectrum of cutaneous human papillomavirus infections at the intersection of genetic variability of viral and human genomes. *J Invest Dermatol*. 2022;142(5):1265-1269.
159. de Oliveira WR, Festa Neto C, Rady PL, Tyring SK. Clinical aspects of epidermodysplasia verruciformis. *J Eur Acad Dermatol Venereol*. 2003;17(4):394-398.
160. Nuovo GJ, Ishag M. The histologic spectrum of epidermodysplasia verruciformis. *Am J Surg Pathol*. 2000;24(10):1400-1406.
161. Gul U, Kilic A, Gonul M, Cakmak SK, Bayis SS. Clinical aspects of epidermodysplasia verruciformis and review of the literature. *Int J Dermatol*. 2007;46(10):1069-1072.
162. Saeidian AH, Youssefian L, Naji M, et al. Whole transcriptome-based skin virome profiling in typical epidermodysplasia verruciformis reveals alpha-, beta-, and gamma-HPV infections. *JCI Insight*. 2023;8(5):e162558.
163. Uddin KMF, Amin R, Majumder SN, et al. An ANKRD26 nonsense somatic mutation in a female with epidermodysplasia verruciformis (tree man syndrome). *Clin Case Rep*. 2018;6(8):1426-1430.
164. Nowak K, Linzner D, Thrasher AJ, Lambert PF, Di WL, Burns SO. Absence of gamma-chain in keratinocytes alters chemokine secretion, resulting in reduced immune cell recruitment. *J Invest Dermatol*. 2017;137(10):2120-2130.
165. Mace EM. Human natural killer cells: form, function, and development. *J Allergy Clin Immunol*. 2023;151(2):371-385.
166. de Jong SJ, Crequer A, Matos I, et al. The human CIB1-EVER1-EVER2 complex governs keratinocyte-intrinsic immunity to beta-papillomaviruses. *J Exp Med*. 2018;215(9):2289-2310.
167. Zhao Z, Wu Y, Zhou Z, et al. ALA-PDT successfully treated multiple cSCC in situ and AK in a patient with epidermodysplasia verruciformis. *Photodiagnosis Photodyn Ther*. 2021;35:102395.
168. Gubinelli E, Posteraro P, Cocuroccia B, Girolomoni G. Epidermodysplasia verruciformis with multiple mucosal carcinomas treated with pegylated interferon alfa and acitretin. *J Dermatolog Treat*. 2003;14(3):184-188.
169. Anadolu R, Oskay T, Erdem C, Boyvat A, Terzi E, Gurgey E. Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa-2a. *J Am Acad Dermatol*. 2001;45(2):296-299.
170. McDermott DH, Pastrana DV, Calvo KR, et al. Plerixafor for the treatment of WHIM syndrome. *N Engl J Med*. 2019;380(2):163-170.
171. Henrickson SE, Treat JR. Topical Cidofovir for recalcitrant verrucae in individuals with severe combined immunodeficiency after hematopoietic stem cell transplantation. *Pediatr Dermatol*. 2017;34(1):e24-e25.
172. Moffatt S, Yaegashi N, Tada K, Tanaka N, Sugamura K. Human parvovirus B19 nonstructural (NS1) protein induces apoptosis in erythroid lineage cells. *J Virol*. 1998;72(4):3018-3028.
173. Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *J Intern Med*. 2006;260(4):285-304.
174. Hayakawa H, Tara M, Niina K, Osame M. A clinical study of adult human parvovirus B19 infection. *Intern Med*. 2002;41(4):295-299.
175. Simmons R, Sharp C, McClure CP, et al. Parvovirus 4 infection and clinical outcome in high-risk populations. *J Infect Dis*. 2012;205(12):1816-1820.
176. Benjamin LA, Lewthwaite P, Vasanthapuram R, et al. Human parvovirus 4 as potential cause of encephalitis in children, India. *Emerg Infect Dis*. 2011;17(8):1484-1487.
177. Heegaard ED, Petersen BL, Heilmann CJ, Hornsleth A. Prevalence of parvovirus B19 and parvovirus V9 DNA and antibodies in paired bone marrow and serum samples from healthy individuals. *J Clin Microbiol*. 2002;40(3):933-936.
178. Seyama K, Kobayashi R, Hasle H, et al. Parvovirus B19-induced anemia as the presenting manifestation of X-linked hyper-IgM syndrome. *J Infect Dis*. 1998;178(2):318-324.
179. Grammatikos A, Donati M, Johnston SL, Gompels MM. Peripheral B cell deficiency and predisposition to viral infections: the paradigm of immune deficiencies. *Front Immunol*. 2021;12:731643.
180. Zanelli M, Ruggeri L, Sanguedolce F, et al. Parvovirus B19 infection in a patient with common variable immunodeficiency. *Mediterr J Hematol Infect Dis*. 2021;13(1):e2021026.
181. Kurtzman GJ, Ozawa K, Cohen B, Hanson G, Oseas R, Young NS. Chronic bone marrow failure due to persistent B19 parvovirus infection. *N Engl J Med*. 1987;317(5):287-294.
182. Naides SJ, Scharosch LL, Foto F, Howard EJ. Rheumatologic manifestations of human parvovirus B19 infection in adults. Initial two-year clinical experience. *Arthritis Rheum*. 1990;33(9):1297-1309.
183. Cassinotti P, Siegl G, Michel BA, Bruhlmann P. Presence and significance of human parvovirus B19 DNA in synovial membranes and bone marrow from patients with arthritis of unknown origin. *J Med Virol*. 1998;56(3):199-204.
184. Adams ST, Schmidt KM, Cost KM, Marshall GS. Common variable immunodeficiency presenting with persistent parvovirus B19 infection. *Pediatrics*. 2012;130(6):e1711-e1715.
185. Watanabe T, Kawashima H. Acute encephalitis and encephalopathy associated with human parvovirus B19 infection in children. *World J Clin Pediatr*. 2015;4(4):126-134.
186. Nolan RC, Chidlow G, French MA. Parvovirus B19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for human immunodeficiency virus infection. *Clin Infect Dis*. 2003;36(9):1191-1194.
187. Christensen LS, Hoiby N. Parvovirus B19–a cause of hepatitis in patients with liver transplantation, anemia in HIV positive individuals and encephalopathies in children. *Ugeskr Laeger*. 1998;160(11):1653.
188. Strenger V, Merth G, Lackner H, et al. Malignancy and chemotherapy induced haemophagocytic lymphohistiocytosis in children and adolescents-a single Centre experience of 20 years. *Ann Hematol*. 2018;97(6):989-998.
189. Moritake H, Kamimura S, Nunoi H, et al. Clinical characteristics and genetic analysis of childhood acute lymphoblastic leukemia with hemophagocytic lymphohistiocytosis: a Japanese retrospective study by the Kyushu-Yamaguchi Children's cancer study group. *Int J Hematol*. 2014;100(1):70-78.
190. Drago E, Garbarino F, Signa S, et al. Case report: susceptibility to viral infections and secondary hemophagocytic lymphohistiocytosis responsive to intravenous immunoglobulin as primary manifestations of adenosine deaminase 2 deficiency. *Front Immunol*. 2022;13:937108.
191. Bird JA, McClain KL, Rosenblatt HM, Abramson SL, Hanson IC. Hemophagocytic lymphohistiocytosis in a patient with

x-linked lymphoproliferative disease. *Allergy Asthma Proc*. 2009;30(4):458-462.
192. Zhong Q, Zeng J, Lin T, Song T. The detection, treatment of parvovirus B19 infection induced anemia in solid organ transplants: a case series and literature review of 194 patients. *Transfus Clin Biol*. 2022;29(2):168-174.
193. Holterhus M, Hennies M, Hillmann H, et al. Parvovirus B19 infection in pediatric allogeneic hematopoietic cell transplantation—single-center experience and review. *Transpl Infect Dis*. 2023;25(2):e14028.
194. Thibile S, Barrett C, Potgieter S, Joubert G, Malherbe J. Adult pure red cell aplasia at Universitas academic hospital, Bloemfontein, South Africa: a 9-year review. *S Afr Med J*. 2022;112(9):753-759.
195. Keramari S, Poutoglidis A, Chatzis S, Keramaris M, Savopoulos C, Kaiafa G. Parvovirus B19-associated myocarditis: A literature review of pediatric cases. *Cureus*. 2022;14(1):e21726.
196. Rodriguez-Espinosa D, Esforzado N, Hermida E, et al. A case of recurrent anemia due to chronic parvovirus B19 infection in a kidney transplant recipient. Can everolimus make a difference? *CEN Case Rep*. 2021;10(3):388-392.
197. Zhang SY. Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. *Hum Genet*. 2020;139(6–7):911-918.
198. Ogunjimi B, Zhang SY, Sorensen KB, et al. Inborn errors in RNA polymerase III underlie severe varicella zoster virus infections. *J Clin Invest*. 2017;127(9):3543-3556.
199. Meyts I, Bucciol G, Jansen K, Wollants E, Breuer J. Aichivirus: an emerging pathogen in patients with primary and secondary B-cell deficiency. *J Clin Immunol*. 2023;43(3):532-535.
200. Mayor PC, Eng KH, Singel KL, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States immune deficiency network registry. *J Allergy Clin Immunol*. 2018;141(3):1028-1035.
201. McLaughlin-Drubin ME, Munger K. Viruses associated with human cancer. *Biochim Biophys Acta*. 2008;1782(3):127-150.
202. Chen ML, Wang SH, Wei JC, Yip HT, Hung YM, Chang R. The impact of human papillomavirus infection on skin cancer: a population-based cohort study. *Oncologist*. 2021;26(3):e473-e483.
203. Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. *J Allergy Clin Immunol*. 2018;141(1):59-68 e54.
204. Harwood CA, Surentheran T, Sasieni P, et al. Increased risk of skin cancer associated with the presence of epidermodysplasia verruciformis human papillomavirus types in normal skin. *Br J Dermatol*. 2004;150(5):949-957.
205. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. *Microbiol Mol Biol Rev*. 2009;73(2):348-370.
206. de Jong SJ, Imahorn E, Itin P, et al. Epidermodysplasia verruciformis: inborn errors of immunity to human beta-papillomaviruses. *Front Microbiol*. 2018;9:1222.
207. Partridge ME, Pariser RJ. Ocular and cutaneous squamous cell carcinoma in an African American man with epidermodysplasia verruciformis resulting in blindness and death. *J Am Acad Dermatol*. 2003;49(5 Suppl):S262-S264.
208. Lazarczyk M, Dalard C, Hayder M, et al. EVER proteins, key elements of the natural anti-human papillomavirus barrier, are regulated upon T-cell activation. *PloS One*. 2012;7(6):e39995.
209. Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. *Semin Immunol*. 2006;18(6):362-374.
210. Lazarczyk M, Pons C, Mendoza JA, Cassonnet P, Jacob Y, Favre M. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. *J Exp Med*. 2008;205(1):35-42.
211. Howley PM, Pfister HJ. Beta genus papillomaviruses and skin cancer. *Virology*. 2015;479-480:290-296.
212. Hufbauer M, Lazic D, Akgul B, Brandsma JL, Pfister H, Weissenborn SJ. Enhanced human papillomavirus type 8 oncogene expression levels are crucial for skin tumorigenesis in transgenic mice. *Virology*. 2010;403(2):128-136.
213. Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, Murphy PM. WHIM syndrome: from pathogenesis towards personalized medicine and cure. *J Clin Immunol*. 2019;39(6):532-556.
214. Pastrana DV, Peretti A, Welch NL, et al. Metagenomic discovery of 83 new human papillomavirus types in patients with immunodeficiency. *mSphere*. 2018;3(6):e00645-18.
215. Gulino AV. WHIM syndrome: a genetic disorder of leukocyte trafficking. *Curr Opin Allergy Clin Immunol*. 2003;3(6):443-450.
216. Meuris F, Carthagena L, Jaracz-Ros A, et al. The CXCL12/CXCR4 signaling pathway: a new susceptibility factor in human papillomavirus pathogenesis. *PLoS Pathog*. 2016;12(12):e1006039.
217. Dotta L, Notarangelo LD, Moratto D, et al. Long-term outcome of WHIM syndrome in 18 patients: high risk of lung disease and HPV-related malignancies. *J Allergy Clin Immunol Pract*. 2019;7(5):1568-1577.
218. Beaussant Cohen S, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French severe chronic Neutropenia registry. *Orphanet J Rare Dis*. 2012;7:71.
219. Su HC. Dedicator of cytokinesis 8 (DOCK8) deficiency. *Curr Opin Allergy Clin Immunol*. 2010;10(6):515-520.
220. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med*. 2009;361(21):2046-2055.
221. Aydin SE, Kilic SS, Aytekin C, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options—a review of 136 patients. *J Clin Immunol*. 2015;35(2):189-198.
222. Cekic S, Metin A, Aytekin C, et al. The evaluation of malignancies in Turkish primary immunodeficiency patients; a multicenter study. *Pediatr Allergy Immunol*. 2020;31(5):528-536.
223. Sasihuseyinoglu AS, Yilmaz M, Altintas DU, et al. Squamous cell carcinoma with hyper-IgE syndrome: A case report. *J Pediatr Hematol Oncol*. 2018;40(6):e380-e382.
224. Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. *Arch Dermatol*. 2012;148(1):79-84.
225. Papa R, Penco F, Volpi S, Gattorno M. Actin remodeling defects leading to autoinflammation and immune dysregulation. *Front Immunol*. 2020;11:604206.
226. Hsu AP, Sampaio EP, Khan J, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood*. 2011;118(10):2653-2655.
227. Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood*. 2014;123(6):809-821.
228. Dickinson RE, Griffin H, Bigley V, et al. Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. *Blood*. 2011;118(10):2656-2658.
229. Hsu AP, Johnson KD, Falcone EL, et al. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. *Blood*. 2013;121(19):3830-3837, S3831-3837.
230. Wlodarski MW, Hirabayashi S, Pastor V, et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood*. 2016;127(11):1387-1397; quiz 1518.

231. Parta M, Cole K, Avila D, et al. Hematopoietic cell transplantation and outcomes related to human papillomavirus disease in GATA2 deficiency. *Transplant Cell Ther*. 2021;27(5):435.e1-435.e11.
232. Abdollahpour H, Appaswamy G, Kotlarz D, et al. The phenotype of human STK4 deficiency. *Blood*. 2012;119(15):3450-3457.
233. Saglam A, Cagdas D, Aydin B, et al. STK4 deficiency and EBV-associated lymphoproliferative disorders, emphasis on histomorphology, and review of literature. *Virchows Arch*. 2022;480(2):393-401.
234. Schipp C, Schlutermann D, Honscheid A, et al. EBV negative lymphoma and autoimmune lymphoproliferative syndrome like phenotype extend the clinical spectrum of primary immunodeficiency caused by STK4 deficiency. *Front Immunol*. 2018;9:2400.
235. Sherkat R, Sabri MR, Dehghan B, et al. EBV lymphoproliferative-associated disease and primary cardiac T-cell lymphoma in a STK4 deficient patient: a case report. *Medicine (Baltimore)*. 2017;96(48):e8852.
236. Morgan EL, Patterson MR, Ryder EL, et al. MicroRNA-18a targeting of the STK4/MST1 tumour suppressor is necessary for transformation in HPV positive cervical cancer. *PLoS Pathog*. 2020;16(6):e1008624.
237. Howard A, Bojko J, Flynn B, Bowen S, Jungwirth U, Walko G. Targeting the hippo/YAP/TAZ signalling pathway: novel opportunities for therapeutic interventions into skin cancers. *Exp Dermatol*. 2022;31(10):1477-1499.
238. Mansour S, Josephs KS, Ostergaard P, et al. Redefining WILD syndrome: a primary lymphatic dysplasia with congenital multisegmental lymphoedema, cutaneous lymphovascular malformation, CD4 lymphopaenia and warts. *J Med Genet*. 2023;60(1):84-90.
239. El Kettani A, Ailal F, El Bakkouri J, et al. HPV-related skin phenotypes in patients with inborn errors of immunity. *Pathogens*. 2022;11(8):857.
240. de Oliveira WR, da Cruz Silva LL, Neto CF, Tyring S. Deleterious effect of radiation therapy on epidermodysplasia verruciformis patients. *J Cutan Med Surg*. 2015;19(4):416-421.
241. Rajabi MT, Ghasemi H, Safizadeh M, et al. Conjunctival squamous cell carcinoma with intraocular invasion after radiotherapy in epidermodysplasia verruciformis. *Can J Ophthalmol*. 2014;49(2):e43-e46.
242. Spurgeon ME, Lambert PF. Merkel cell polyomavirus: a newly discovered human virus with oncogenic potential. *Virology*. 2013;435(1):118-130.
243. Tolstov YL, Pastrana DV, Feng H, et al. Human Merkel cell polyomavirus infection II. MCV is a common human infection that can be detected by conformational capsid epitope immunoassays. *Int J Cancer*. 2009;125(6):1250-1256.
244. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol*. 2008;58(3):375-381.
245. Harms KL, Healy MA, Nghiem P, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system. *Ann Surg Oncol*. 2016;23(11):3564-3571.
246. Becker JC. Merkel cell carcinoma. *Ann Oncol*. 2010;21 Suppl 7:vii81-vii85.
247. Kouzmina M, Koljonen V, Leikola J, Bohling T, Lantto E. Frequency and locations of systemic metastases in Merkel cell carcinoma by imaging. *Acta Radiol Open*. 2017;6(3):2058460117700449.
248. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol*. 2003;49(5):832-841.
249. Garneski KM, Warcola AH, Feng Q, Kiviat NB, Leonard JH, Nghiem P. Merkel cell polyomavirus is more frequently present in north American than Australian Merkel cell carcinoma tumors. *J Invest Dermatol*. 2009;129(1):246-248.
250. Ma JE, Brewer JD. Merkel cell carcinoma in immunosuppressed patients. *Cancers (Basel)*. 2014;6(3):1328-1350.
251. Starrett GJ, Marcelus C, Cantalupo PG, et al. Merkel cell polyomavirus exhibits dominant control of the tumor genome and transcriptome in virus-associated Merkel cell carcinoma. *MBio*. 2017;8(1):e02079-16.
252. Hesbacher S, Pfitzer L, Wiedorfer K, et al. RB1 is the crucial target of the Merkel cell polyomavirus large T antigen in Merkel cell carcinoma cells. *Oncotarget*. 2016;7(22):32956-32968.
253. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. *J Clin Oncol*. 2002;20(2):588-598.
254. Crall C, Morley KW, Rabinowits G, Schmidt B, Dioun Broyles A, Huang JT. Merkel cell carcinoma in a patient with GATA2 deficiency: a novel association with primary immunodeficiency. *Br J Dermatol*. 2016;174(1):169-171.
255. Recher M, Karjalainen-Lindsberg ML, Lindlof M, et al. Genetic variation in schlafen genes in a patient with a recapitulation of the murine Elektra phenotype. *J Allergy Clin Immunol*. 2014;133(5):1462-1465, 1465 e1461-1465.
256. Oliveira WR, Sotto MN, Festa C, Rady P, Tyring SK. Merkel cell polyomavirus in Merkel cell carcinoma from a Brazilian epidermodysplasia verruciformis patient. *J Am Acad Dermatol*. 2010;62(5):889-890.
257. Mizuno Y, Kato G, Shu E, et al. Merkel cell polyomavirus-positive Merkel cell carcinoma in a patient with epidermodysplasia verruciformis. *Acta Derm Venereol*. 2015;95(1):98-99.
258. Mertz KD, Schmid M, Burger B, et al. Detection of Merkel cell polyomavirus in epidermodysplasia-verruciformis-associated skin neoplasms. *Dermatology*. 2011;222(1):87-92.
259. Scott MP, Helm KF. Cytokeratin 20: a marker for diagnosing Merkel cell carcinoma. *Am J Dermatopathol*. 1999;21(1):16-20.
260. Siqueira SOM, Campos-do-Carmo G, Dos Santos ALS, Martins C, de Melo AC. Merkel cell carcinoma: epidemiology, clinical features, diagnosis and treatment of a rare disease. *An Bras Dermatol*. 2023;98(3):277-286.
261. Lewis DJ, Sobanko JF, Etzkorn JR, et al. Merkel cell carcinoma. *Dermatol Clin*. 2023;41(1):101-115.
262. Park SY, Doolittle-Amieva C, Moshiri Y, et al. How we treat Merkel cell carcinoma: within and beyond current guidelines. *Future Oncol*. 2021;17(11):1363-1377.
263. Whitley R, Baines J. Clinical management of herpes simplex virus infections: past, present, and future. *F1000Res*. 2018;7:1726.
264. Looker KJ, Johnston C, Welton NJ, et al. The global and regional burden of genital ulcer disease due to herpes simplex virus: a natural history modelling study. *BMJ Glob Health*. 2020;5(3):e001875.
265. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. *Neurotherapeutics*. 2016;13(3):493-508.
266. Steiner I, Benninger F. Update on herpes virus infections of the nervous system. *Curr Neurol Neurosci Rep*. 2013;13(12):414.
267. Wang L, Wang R, Xu C, Zhou H. Pathogenesis of herpes stromal keratitis: immune inflammatory response mediated by inflammatory regulators. *Front Immunol*. 2020;11:766.
268. Beasley KL, Cooley GE, Kao GF, Lowitt MH, Burnett JW, Aurelian L. Herpes simplex vegetans: atypical genital herpes infection in a patient with common variable immunodeficiency. *J Am Acad Dermatol*. 1997;37(5 Pt 2):860-863.
269. Delgado-Marquez AM, Zarco C, Ruiz R, Simarro A, Vanaclocha F. Severe disseminated primary herpes simplex infection as skin manifestation of GATA2 deficiency. *J Eur Acad Dermatol Venereol*. 2016;30(7):1248-1250.
270. Parsons K, Cipriano SD, Rosen LB, et al. Severe facial herpes vegetans and viremia in NFKB2-deficient common variable immunodeficiency. *Front Pediatr*. 2019;7:61.
271. Spinner MA, Ker JP, Stoudenmire CJ, et al. GATA2 deficiency underlying severe blastomycosis and fatal herpes simplex virus-associated hemophagocytic lymphohistiocytosis. *J Allergy Clin Immunol*. 2016;137(2):638-640.

272. Jasim A, Proietto A, Scurry J. Herpes simplex virus infection of vulvar squamous cell carcinoma. *Pathology*. 2016;48(1):80-81.
273. Alibek K, Baiken Y, Kakpenova A, et al. Implication of human herpesviruses in oncogenesis through immune evasion and supression. *Infect Agent Cancer*. 2014;9(1):3.
274. Strehl JD, Mehlhorn G, Koch MC, et al. HIV-associated hypertrophic herpes simplex genitalis with concomitant early invasive squamous cell carcinoma mimicking advanced genital cancer: case report and literature review. *Int J Gynecol Pathol*. 2012;31(3):286-293.
275. Ronkainen SD, Rothenberger M. Herpes vegetans: an unusual and acyclovir-resistant form of HSV. *J Gen Intern Med*. 2018;33(3):393.
276. Akbari M, Elmi R. Herpes simplex virus and human papillomavirus coinfections in hyperimmunoglobulin E syndrome presenting as a conjunctival mass lesion. *Case Rep Med*. 2017;2017:1650841.
277. Blieden LS, Chevez-Barrios P, Yen MT. Herpes simplex vegetans presenting as an eyelid mass. *Ophthalmic Plast Reconstr Surg*. 2011;27(3):e58-e59.
278. Magg T, Schober T, Walz C, et al. Epstein-Barr virus(+) smooth muscle tumors as manifestation of primary immunodeficiency disorders. *Front Immunol*. 2018;9:368.
279. Beziat V, Jouanguy E. Human inborn errors of immunity to oncogenic viruses. *Curr Opin Immunol*. 2021;72:277-285.

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