Feb 86

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MCRH) (1,2), also known under other terms such as lipoid dermatoarthritis, is a rarely diagnosed disease characterized by cutaneous and mucosal nodules and a destructive arthropathy. Skin nodules are common on the hands but can be generalized. Bone and a variety of other tissues can also be involved. Diagnosis is usually by biopsy of a skin nodule showing the typical large histiocytes and giant cells with ground glass or foamy eosinophilic cytoplasm. Multiple large and small joints are involved in a progressive symmetrical erosive arthritis that mimics RA. DIP involvement however is very common; severe arthritis mutilans may be seen. The course is unpredictable and the disease may remit. Women are affected more often than men. Disease etiology and even the composition of the expanded histiocyte cytoplasm is not established (1,2). Glycoproteins or lipids have been suggested in different series as components of the infiltrating cells. Sedimentation rates are only mildly elevated and no characteristic tests on serum have been reported. Specifically rheumatoid factor and lipid levels are normal.

No treatment has been predictably effective. Gold, penicillamine or immunosuppressives may have helped some patients.

Synovial Fluid Analyses

Ref	Vol (cc)	Viscosity or mucin clot	RBC/mm^3	WBC/mm^3	P%	M%	L%	"Foam cells"
2	25-30	Fair	6000-15,200	1800-2400	2-5	30-53	27-54	11-16%
3				20,000	90			
4		Poor	1000-21,220	30,000-93,000				
11		Poor	many			46	28	many
12				500-5150	10-26			
13		Poor		220-520	9-18	36-37	35-42	

Freemont et al (13) saw some huge cells in a joint fluid but most others have

not. These cells were strongly positive with non-specific esterase suggesting a monocyte origin. We noted cells with profuse cytoplasmic filaments and coated pits in fluid of 1 case studied by EM. These were similar to findings in some deep synovial cells. Such cytoplasmic filaments are seen in monocytes.

Gross Descriptions Gross appearance of synovium has not been published.

Light microscopy (1,2,5,6,7,8,13) Synovial villi are proliferated. Large histiocytic cells infiltrate immediately beneath and sometimes among the synovial lining layer cells (Fig. 1). Cells measure up to 60 u in diameter and have eosinophilic "ground glass" or foamy cytoplasm. Most such cells are mononuclear but multinucleated cells can be seen; these multinucleated giant cells appear to be less common than in the skin.

Other features described include prominent vascularity (1,2,7), venous obliteration(5), edema, extravasated erythrocytes, and intimal thickening of vessel walls. Infiltration with small numbers of normal sized macrophages, lymphocytes and plasma cells has also been noted (1,2). Surface fibrin was described in 1 report (13).

Histochemical staining of the large histiocytes has been reported to show PAS positivity in most studies and variable results on staining for neutral fats (1,2). PAS stained material has been diastase resistant. Occasional iron staining has been noted (7).

Electron microscopy

Only limited EM studies have been reported. The presence of giant cells can be confirmed (Fig. 2). They contain many vacuoles and mitochondria. We (11) and Krey et al (2) found large vacuoles (Fig. 2) in the histiocytes that appeared empty or with a finely granular material. The vacuoles seemed closely related to smooth endoplasmic reticulum and to the Golgi apparatus. Rough ER seems to be sparse. Mitochondria were seen adjacent to the vacuoles in her case and this was

even more prominent in a case studied in my laboratory where mitochondria tended to partially wrap around some vacuoles (Fig. 3a). There was a fine granularity in or on the interior surface of some vacuole like structures (Fig. 3). Bregeon et al showed similar findings (14). The cytoplasm of some cells with and without vacuoles has been especially rich in filaments (Fig. 4). Coated pits were prominent in our case. Endothelial cells are prominent. Occasional phagocytized material including erythrocytes was seen in some macrophages. Laminated inclusions have also been noted (2). Varying numbers of acid phosphatase positive lysosomes are reported (13).

Synovial lining cells in these patients have been mostly those rich in rough endoplasmic reticulum but without the vacuoles seen in the large cells.

Other published EMs do not clearly identify the site of origin of the illustrated cells but show either vacuoles or rough ER containing cells (1,4).

Implications

This disease should be distinguishable from RA and other arthritides when the typical skin lesions are noted and biopsied. Synovial biopsy may also lead to an initial diagnosis although synovial lesions may be less typical than the skin infiltrates. However, rheumatoid arthritis or pigmented villonodular synovitis could be confused (with their giant cells and inflammation) on a histologic as well as a clinical basis. Rheumatoid giant cells as described by light microscopy are very similar to those seen here. They are usually less prominent than in the severe MCRH cases. Iron found in some patients with multicentric reticulocytosis is probably a result of red cell extravastion but along with giant cells could lead to confusion with pigmented villonodular synovitis. The latter disease is usually monoarticular. One can not be certain that some reported cases of MCRH will not later be proven to have some other such disease. There does appear to be a diversity in reported cases including very

prominently inflammatory synovial fluids in some suggesting a component other than that of a primarily infiltrative disease. Multicentric reticulo-histiocytosis seems to be distinct from other histiocytic diseases such as Gaucher's disease, the histiocytosis X group ( ), a even less common familial histiocytic dermatoarthritis (9) with smaller fibroblastic cells and from xanthomas (10). Foam cells are much more common in xanthomas. Histologic findings may have similarities with the histiocytosis X group but clinical pictures are very different.

So far there are few clues to etiology. Associated diseases have shown no helpful pattern. There is an unexplained increased risk of associated malignancy. The present concensus seems to be that this is a deposition disease with reaction to the still unidentified abnormal material in the vacuoles. Much of this material seems to be dissolved out or otherwise lost in electron micrographs. What remains is not osmiophilic as neutral fat and phospholipid would be. The EM appearance and PAS positivity suggests that it might be a glycoprotein (2). One immunoperoxidase study of skin lesions in a patient who had a typical MCRH with a paraprotein showed immuno-globulins in vacuoles (15).

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Legends

Fig. 1

Large cells with eosinophilic cytoplasm occupy parts of the synovial surface but are most prominent in the deeper synovium. JS=joint space ____X. Hematoxylin and eosin

Fig. 2

Giant cell in deep synovium with many vacuoles and prominent dark mitochondria. N=Nucleus with large nucleolus. Electron micrograph ____X

Fig. 3a

Mitochondria curve around the margin of some vacuoles ____X

Fig. 3b

Vacuoles can be seen to contain small amounts of very finely granular material partially adhering to the vacuole membrane ____X.

Fig. 4

Cytoplasmic filaments are markedly increased in some cells. Electron micrograph ____X