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Joint fluid cytology in Reiter's disease

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SUMMARY The diagnostic value of the finding of cytophagocytic macrophages (CPM) in the joint fluid of patients with Reiter's disease has been re-examined. CPM were found in 46% of Reiter's disease fluids and in 45% of other inflammatory knee joint fluids. Higher CPM scores, on a 4-point grading, were commoner in Reiter's disease but the difference was not statistically significant. Further, although the graded polymorphonuclear leucocyte phagocytosis shown by CPM was greater in Reiter's disease this also was not significant. It is concluded that the presence of CPM in joint fluid is of little discriminating value.

Traditionally the diagnosis of Reiter's disease has been based upon the clinical triad of non-specific urethritis, arthritis usually affecting the knees and ankles, and conjunctivitis. Routine laboratory investigations have not been helpful. However, it has been accepted that conjunctivitis may be absent and with the recent finding that the majority of these patients are HLA B27 positive (Brewerton, 1975), some authors have advocated the inclusion of even less complete cases into the diagnostic category of Reiter's disease (Arnett *et al.*, 1976).

Pekin *et al.* (1967) found large macrophages which had phagocytosed one or more polymorphonuclear leucocytes in the synovial fluid of all 11 of their cases of Reiter's disease but in only 2 of more than 200 other samples of inflammatory synovial fluids. Since there have been no further reports of this finding which if confirmed, could be a very useful test, we have re-examined its diagnostic value.

Material and methods

There were 39 knee-joint fluids from 20 patients (15 M : 5 F) with Reiter's disease. In 7 patients the fluid from both knee joints was examined, often some days apart, while the remaining 12 fluids represent repeat aspirations of the same knee joint in 8 patients. All patients had non-specific urethritis and arthritis, while 9 had conjunctivitis, 3 mouth ulceration, and 1 keratoderma blennorrhagica. All patients had active disease with a marked synovial reaction, general malaise, and low grade fever. At the time of joint aspiration all were receiving non-steroidal anti-inflammatory drugs while 9 were completing a 10–21 day course of oxytetracycline. The mean haemoglobin concentration was 13·0 g/dl (range 10·9–15·0) and the mean erythrocyte sedimentation rate (Westergren) was 49·2 mm/hour (range 3–135) at the time of joint aspiration. The joint fluid was obtained a mean of 2·5 weeks (range 1 day to 8 weeks) after the appearance of symptoms and signs in the target joint. Gonococcal arthritis and other forms of sero-negative polyarthritis (Wright *et al.*, 1977) were excluded as the cause of the arthritis. HLA typing was not undertaken.

There were 20 synovial fluids from the knee joints of 16 patients known to have acute inflammatory joint disease of unknown cause. These fluids were selected since they were known to be free of bacteria and to contain large numbers of polymorphonuclear leucocytes. These patients were followed for a mean of 2 years (range 6 months–5 years) to exclude Reiter's disease as the diagnosis. The final diagnoses were rheumatoid arthritis (6), ankylosing spondylitis (2), psoriatic arthritis (2), erythema nodosum and arthritis (2), viral arthritis (2), calcium pyrophosphate crystal arthritis (1), and unknown (1).

Joint fluids were centrifuged at 2000 rpm for about 5 min, and the supernatant fluid poured off. The cell sediment was transferred, without dilution, to a clean glass slide and spread with the edge of another slide. The smears were processed in two different ways; wet-fixed smears were stained by a standard Papanicolaou schedule, and rapidly air-dried smears were fixed in methyl alcohol and stained with May-Grunwald and Giemsa.

Two observers (A.I.S. and M.M.B.) independently

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and blindly scored smears from each sample for two separate features; first, the frequency of cytophagocytic macrophages (CPM), and secondly, the numbers of polymorphonuclear leucocytes within any one macrophage. These scores were not based upon counts, which would have been extremely laborious, but on assessments made according to the following scheme:

	Numbers of CPM
0	None
+	One or a few per slide
++	Easily found but not numerous
+++	Numerous or abundant

	Numbers of polymorphs ingested
+	Single only
++	Mostly single, one or a few multiple
+++	Numbers of CPM contain multiple polymorphs

The two observers did not collaborate beforehand in trial runs to achieve consistent scoring. Differences in scoring are mainly due to variations in judgment about whether or not to accept a macrophage containing digested cell remnants, when the morphological features of polymorphs have almost disappeared. Pekin *et al.* (1967) described their characteristic cells as unusually large (40 μm diameter), with 'one or more intact polymorphonuclear leucocytes and deeper staining basophilic globular structures within the cytoplasm'. Since the ingested leucocytes age hardly ever 'intact', and since the debris of digested cells is the main content in the cells which Pekin *et al.* (1967) illustrated, we have used the semi-quantitative scoring described above rather than the presence or absence of "characteristic" cells (see Figs. 1 and 2).

Statistical significance was assessed using Fisher's exact one-tail test.

Results

There was a fairly good correlation between the gradings by the two observers for both of the features scored, as in all but 3 cases the disagreement was by one grade.

The comparative gradings of the joint fluids for the presence of CPM are shown in Table 1. Eighteen of the 39 (46%) Reiter's disease fluids were scored positive by both observers compared with 9 of the 20 (45%) control fluids. If the positive findings by a single observer are included the numbers rise to 26 (68%) and 12 (60%), respectively. Higher scores were commoner in Reiter's disease, both observers scoring ++ or +++ in 8 of 39 (20%) of Reiter's disease fluids, compared with only one of 20 (5%) of the controls; this was not significant ($P<0.15$).

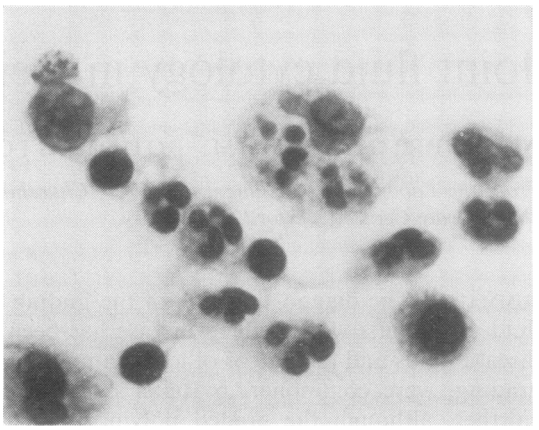

Fig. 1

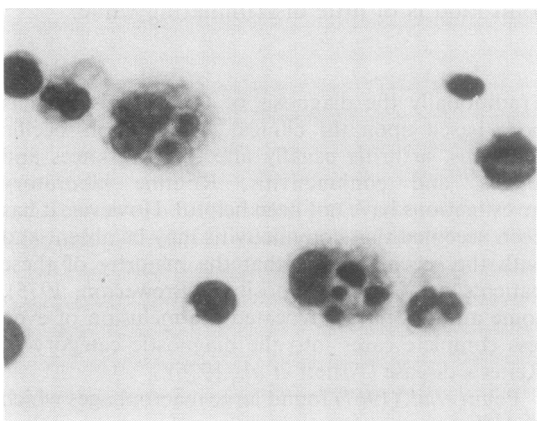

Fig. 2

Figs. 1 and 2 *Cytophagocytic macrophages (CPM) together with lymphocytes and neutrophils.* (×1600.)

The comparative gradings of the joint findings for

Table 1 *Comparative gradings of CPM*

Observer B	*Observer A*			
	0	+	++	+++
Reiter's disease				
0	13	4		
+	4	4	5	1
++			3	2
+++			1	2
Controls				
0	8	1	1	
+	1	6	1	1
++				1
+++				

Table 2 *Comparative gradings of ingested polymorphs*

Observer B	*Observer A*			
	0	+	++	+++
Reiter's disease				
0		4		
+	4	5	2	4
++			2	2
+++				3
Controls				
0		2		
+	1	4	1	2
++		1		
+++				1

numbers of leucocytes ingested are shown in Table 2. The absence of CPM naturally excluded a scoring for this. The degree of phagocytosis was not significantly greater in the patients with Reiter's disease, even though 7 of the 18 fluids were graded ++ or +++ by both observers, compared with 1 of 9 of the control fluids ($P<0\cdot11$).

In the 7 patients with Reiter's disease in whom fluid from both knee joints was examined within a few days, CPM showing a similar degree of polymorph phagocytosis were found in 4 cases but were absent in the remaining three. Among the controls there were 2 patients who had had simultaneous aspiration of both knees, and CPM were found in both specimens from 1 patient.

In the patients with Reiter's disease there was no correlation between the joint fluid findings and the patient's age, sex, haemoglobin value, erythrocyte sedimentation rate, the duration of the disease, the duration of symptoms in the target joint, or the presence of additional clinical features particularly conjunctivitis.

Discussion

In any syndrome whose causal mechanism is unknown, it is desirable to have some laboratory test which, ideally, should be specific and therefore capable of identifying incomplete or unusual forms of the syndrome. Unfortunately, in the absence of independent criteria by which to ascertain the specificity and sensitivity of such a test, it can only be added to the constellation of features already used in attaching the label.

Does the presence of CPM in joint fluid deserve to be included as one of the features of Reiter's disease? Pekin *et al.* (1967) who made the original observation evidently thought so, but our present observations give them little support. The reason for the large discrepancy between our findings is not clear. Both groups of control fluids came from patients with a similar range of inflammatory diseases. However, our controls were specifically chosen as containing numerous polymorphs, and therefore capable of showing the CPM phenomenon, while Pekin *et al.* (1967) did not state the proportion of those in which polymorphonuclear leucocytes were the dominant cell.

The phenomenon is in any case unlikely to be specific, because CPM are common in other sites in many different conditions; they are commonly seen, for instance, in pleural effusions due to a wide variety of causes.

Pekin *et al.* (1967) two control cases in which CPM were observed were examples of early acute joint inflammation; one had gonococcal and the other meningococcal arthritis. Since 7 of their 11 patients with Reiter's disease were examined within 4 days of onset of articular inflammation, and within 2 weeks in the remaining 4, they postulated that CPM might reflect the early synovial response to the presence of certain organisms. Indeed, in 3 patients, sequential examination of fluid from the same joint showed the gradual disappearance of CPM.

In our series, the most striking development of CPM among the control series was in the single patient with pyrophosphate crystal arthritis. In our patients with Reiter's disease, we were unable to show any correlation between the presence of CPM and other features of Reiter's disease, in particular the duration of the arthritis or the duration of arthritis in the aspirated joint. Postive findings were noted up to eight weeks after the onset of joint symptoms and in several cases repeat aspirations gave positive findings after initial negative results. However, it was of interest to find that in 3 patients with Reiter's disease and 1 patient with ankylosing spondylitis both knee joint fluids showed similar cytological findings when examined within a few days of each other. This suggests that perhaps patient characteristics rather than temporal factors are more important although we were unable to determine what these might be. We cannot comment on the possible role of an infective agent on the appearance of CPM in the synovial fluid, since patients with known bacterial arthritis were excluded from the control series.

Pekin *et al.* (1967) also found high levels of total haemolytic complement in the synovial fluid of their cases of Reiter's disease but this also is a non-specific finding (Hedberg, 1967).

Therefore, it must be emphasised that there is so far no specific laboratory or radiographic feature of Reiter's disease and the diagnosis still depends upon a constellation of findings including: the pattern of arthritis which is usually oligoarticular and asymmetrical with chiefly knee and ankle involvement,

'fluffy' periostitis especially of the calcaneum with heel pain, asymmetrical diffuse swelling of digits, inflammation of the axial skeleton usually as sacroilitis, mucocutaneous manifestations such as keratoderma blennorrhagica, oral ulceration and circinate balanitis, weight loss and general malaise, a history of recent venereal infection, and a predilection for young men and for those of HLA B27 type. The presence of CPM in joint fluid is of little discriminating value.

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