Grand Rounds in Rheumatology

Do B cells influence disease progression in chronic synovitis? Lessons from primary hypogammaglobulinaemia

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Abstract

We describe a 62-yr-old male patient with primary hypogammaglobulinaemia (PH) who fulfilled the 1987 American Rheumatism Association/American College of Rheumatology revised diagnostic criteria for rheumatoid arthritis (RA) but, despite persistent symmetrical synovitis, did not develop erosions. Virology studies and blood and synovial fluid (SF) cultures were consistently negative; a search for crystals in the SF was unrevealing. Peripheral blood (PB) B cells were absent, whilst the PB CD3+ cell count was normal. The ratio of naive (CD45RA+) to memory (CD45R0+) cells was also normal (1:1) but the CD4:CD8 ratio was reversed. To our knowledge, this is the first report which combines the immunophenotypic analysis of the PB with that of the SF and synovial membrane (SM). This confirmed the absence of B cells and the reversed CD4:CD8 ratio. However, as in other chronic arthropathies, the SF and SM cellular infiltrate consisted almost exclusively of memory T cells, consistent with the preferential localization of this subset to inflamed tissues. This case indicates that synovitis can proceed persistently in the absence of B cells and that the migratory mechanisms of T cells are not altered. However, the case suggests that the absence of B cells and negativity for rheumatoid factor, combined with an increased presence of CD8+ (suppressor/cytotoxic) T cells in the joint, might contribute to the non-erosive nature of the synovitis.

Key words: Hypogammaglobulinaemia, Chronic arthritis.

Primary hypogammaglobulinaemia (PH) is a heterogeneous disorder characterized by the reduction in or lack of immunoglobulin isotypes in the absence of contributory disorders or offending drugs [2, 3]. It comprises at least two major forms: Bruton’s or X-linked agammaglobulinaemia (XLA) and common variable immunodeficiency (CVID) [2–4]. XLA is usually caused by mutations in the B cell tyrosine kinase gene [5] that impair the transition from pre-B to B cell [6]. Affected males lack or have only few circulating mature B cells and immunoglobulins [5], whilst cellular immunity is mostly normal [4]. Clinical symptoms, consisting mainly of recurrent bacterial infections, usually appear after 6 months of age, when transferred maternal immunoglobulins are largely metabolized [4]. CVID is a syndrome with a variable genetic compon-
erosive, but fulfilled the 1987 American Rheumatism Association/American College of Rheumatology (ARA/ACR) revised diagnostic criteria for RA [1].

Case report

RP, a 62-yr-old Caucasian male, was referred in August 1994 to our Rheumatology Department with a history of intermittently painful knees of 5 yr duration. In the previous few months, however, he had developed overt synovitis affecting the knees, the wrists, the second and third metacarpophalangeal (MCP) joints bilaterally and the right second proximal interphalangeal (PIP) joint. Early morning stiffness was longer than 1 h, and there were no associated skin rashes or genitourinary, gastrointestinal or eye problems. Past medical history revealed insulin-dependent diabetes of 30 yr duration, with associated mild sensory neuropathy and, previously, bilateral frozen shoulder. He had suffered since 1976 from recurrent respiratory tract infections; adult onset bronchiectasis was diagnosed in 1988. In May 1994, decreased serum globulin levels were detected in routine testing and he was consequently diagnosed as suffering from CVID, whereupon he was started on i.v. immunoglobulin (Sandoglobulin 12 g), given in alternate weeks.

Physical examination revealed marked synovial thickening of both wrists as well as modest swelling of the second and third MCP joints bilaterally and of the second PIP joint of the right hand (Fig. 1A). There were large effusions in both knees, which were aspirated, and biopsy from the suprapatellar pouch was taken after informed consent. Some swelling was noted in the ankles; most joints were tender. Systemic examination was unremarkable except for diffuse pulmonary rales and wheezes, and loss of fine touch sensation in both toes related to the patient’s diabetes.

Routine laboratory investigations showed haemoglobin 12.7 g/l, red blood cells 5.4 c/mm³, PLT 334.000 c/mm³ and white blood cells 16.3 c/mm³ (with 77% neutrophils, 17.6% lymphocytes and 5.4% monocytes). The following tests were normal or negative: urea and electrolytes, urate, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyltransferase were elevated at 240 U/l (normal range 5–126) and 299 U/l (normal range 0–60), respectively. Glucose levels were within normal limits for a patient on insulin replacement therapy. All immunoglobulin isotypes were undetectable (IgG <1.2 g/l [normal range 5.4–16.1], IgA <0.5 g/l [normal range 0.9–4], IgM <0.1 g/l [normal range 0.5–2]). The erythrocyte sedimentation rate (ESR) was 2 mm/1st h, whilst C-reactive protein was slightly elevated at 45 mg/dl (normally <30). Rheumatoid factor, antinuclear factor and anti-neutrophil cytoplasmic antibodies were all negative. Liver biopsy revealed mild chronic hepatitis with nodular regenerative hyperplasia, but no evidence of cirrhosis. A bone marrow biopsy, carried out in June 1994, showed very sparse scattered B cells and plentiful T cells in the absence of other abnormalities. X-rays of the hands and wrists demonstrated loss of articular space of the radiocarpal joints and cystic lesions of the carpal bones and of the ulnar styloids bilaterally in the absence of definite erosions.

The immunophenotype of peripheral blood (PB) and SF was evaluated by immunofluorescence and FACScan analysis. Paraffin-embedded cryostat sections of a knee synovium sample were stained for similar analysis. CD3⁺ cells were 69%, while CD4⁺ and CD8⁺ cells were 17 and 53%, respectively, with a reversed CD4:CD8 ratio (Table 1). CD19⁺ cells (B cells) were <1% (Table 1). The patient was started on non-steroidal anti-
inflammatory drug treatment with a good clinical response, and was followed up at regular intervals. Four years after the initial presentation, the clinical symptoms appeared to resolve spontaneously and repeat X-rays showed no erosions or changes in the hands or feet compared with the original films. No clinical or laboratory abnormalities suggestive of new associated or concomitant diseases were noted.

Discussion

Patients with PH are prone to developing different types of arthritis, including septic arthritis [8], arthritis secondary to autoimmune disease [4], and aseptic arthritis [2]. In our case, septic arthritis was ruled out on the basis of the clinical picture and negative vireology studies, as well as repeated negative blood and SF cultures. Similarly, there were no symptoms or signs suggestive of associated autoimmune disease. In contrast, the synovitis, characterized by early morning stiffness lasting longer than 1 h and by symmetrical involvement of more than three joints, including the small joints of the hands, fulfilled the 1987 ARA/ACR revised diagnostic criteria for RA [1].

Is symmetrical polyarthritis associated with hypogammaglobulinaemia true rheumatoid arthritis?

PH-related polyarthritis can resemble RA clinically, as in our case. However, there are a number of features that differentiate these two conditions. PH-related arthritis is most commonly, although not invariably, non-erosive, usually runs a benign course, and can go into remission on immunoglobulin replacement therapy or spontaneously [2, 4, 12, 13]. Rheumatoid factor (RF) is consistently negative, while ESR can be inappropriately low for the inflammatory status due to the lack of B cell products [3, 4]. Additional distinguishing features are the preferential involvement of the large joints and the absence of the extra-articular manifestations typical of RA [2, 4], although RA-like subcutaneous nodules have been described occasionally [14].

What mechanisms may be responsible for the synovitis in hypogammaglobulinaemia?

The clinical differences between polyarthritis due to PH and classical RA suggest that different pathogenic mechanisms are operative. Histologically, PH-related synovitis is characterized, unlike RA, by mild or moderate synovial hypertrophy with a variable lymphocytic infiltrate [4]. Functional and immunohistochemical studies have revealed that synovial lymphocytes are mainly suppressor T cells, in the absence of functionally active B cells/plasma cells [13].

To further characterize the lymphocyte populations, we carried out in our patient a comparative analysis by double immunofluorescence and cytofluorimetry for T- and B-cell-associated CD markers in the PB and in the SF, while a synovial membrane (SM) sample (obtained from knee biopsy) was evaluated for a similar purpose by immunohistochemistry. The markers investigated and the results are shown in Table 1 and Figs 2 and 3. Cells positive for CD19/CD20 (B-cell markers) were <1% both in the PB and in the synovial compartment (SM and SF), suggesting that humoral immunity, while it may be a pathogenic factor in classical seropositive RA, is not essential per se in the development of chronic synovitis [2, 11, 14]. By contrast, CD3+ cells were detected in normal numbers in the PB and in the joints, although the CD4:CD8 ratio was reversed (0.3 in the PB and SF, and 0.5 in the SM [normal range 1.2–3.8]) due to an elevated number of CD8+ cells. This reversed CD4:CD8 ratio has been described in various patients with PH [13, 15], including two patients whose synovitis was characterized by aggregates of lymphocytes that mostly (>95%) carried the CD8 marker. These results are in striking contrast to the histological findings in the synovium of classical RA, where CD4+ lymphocytes prevail over CD8+ T cells in a ratio of 4:1 [4]. In one of the two patients reported above [13], immunoglobulin treatment led to a dramatic clinical improvement paralleled by a decreased PB CD8+ cell count and normalization of the CD4:CD8 ratio, providing indirect support for a role of CD8+ cells in the pathogenesis of synovitis.

Turning to consideration of the other phenotypic
Two-dimensional FACS profiles of PB (left) and SF (right) lymphocytes. (Row 1) Expression of CD4 and CD8. (Row 2) Expression of CD19, a B-cell marker. (Row 3) Expression of CD45R0/CD3. (Row 4) expression of CD45RA/CD3. For percentages of positive cells, see Table 1.
markers expressed by the SF cells of our patient, we found that the synovial lymphocytes overwhelmingly expressed CD45R0 and CD69 (memory/activation markers) [16–18] but not CD45RA [16, 17], L selectin (naive/resting markers) [19] or CLA (cutaneous lymphocyte antigen). This is in keeping with the general concept that memory cells preferentially migrate to peripheral inflamed tissues [16–18], whereas naive cells preferentially recirculate to lymphoid organs [19, 20]. As expected, CLA, the skin’s ‘homing receptor’ [21, 22], was not detected on the SF cells. Thus, T cells appear to migrate normally in the absence of B lymphocytes.

Can the benign course of PH-related synovitis be explained by the particular subsets of lymphocytes involved?

It is tempting to argue that the combination of lack of B cells and the prevalence of activated CD8+ T cells described above may account for the benign course of arthritis secondary to PH. Although this hypothesis is largely speculative, there is some evidence supporting it. In classical RA, CD4+ (B helper) T cells predominate in the synovium over CD8+ cells [4]. B cells synthesize RF actively in the synovium [23], leading to the formation of immune complexes and the activation of the classical complement and inflammatory cascade, with consequent tissue damage [24]. Furthermore, high titres of IgM and IgA RF are associated clinically with more severe and erosive arthritis [23, 25]. Thus, B cells seem to be an important effector system in inducing tissue damage in RA and, conversely, their absence may indicate a better prognosis. CD8+ T-cell involvement, on the other hand, is not thought to be associated with destructive arthritis [26], although it can mediate synovitis [27, 28]. Therefore, although the pathogenesis of our patient’s arthritis remains unknown, we suspect that the lack of B cells and their products and the prevalence of CD8+ T cells may explain, at least in part, its relatively benign course.

References

B cells in chronic synovitis