X-linked agammaglobulinemia and rheumatoid arthritis
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ABSTRACT

The pathogenic role of B cells in rheumatoid arthritis (RA) has recently gained much interest by the marked clinical responses of anti-CD20 therapy in RA. We describe a patient with X-linked agammaglobulinemia (XLA) who presented with an erosive symmetrical polyarthritis with histological features of RA including formation of a destructive pannus. Furthermore, the patient also developed subcutaneous nodules that were histologically indistinguishable from rheumatoid nodules. Surprisingly, lymphocytic infiltrates in both synovium and nodule consisted almost exclusively of CD8+ T cells. Although some peculiar B cell subsets have been described in XLA patients, no B cell subsets could be demonstrated in synovial tissue or the subcutaneous nodule. This case illustrates that classical RA can develop in the absence of mature B cells.

INTRODUCTION

For many years, the role of B cells in the pathogenesis of rheumatoid arthritis (RA) has been debated. Besides the production of RA associated autoantibodies such as the rheumatoid factor and more recently the anti-citrullinated antibodies, no additional data suggested an important role for B cells. This was further substantiated by the ability to induce inflammation and cartilage degradation by isolated RA synovial fibroblasts, in the absence of B cells, in human-SCID mouse co-implantation models (1). More recently, however, an animal model of arthritis was described in which the arthritis was induced by autoantibodies directed against the glycolytic enzyme glucose-6-phosphate isomerase (GPI) (2). Although the prevalence of anti-GPI antibodies in human RA patients appears to be low, this model suggested that under certain conditions RA associated autoantibodies can be arthritogenic (2, 3). The interest in B cell pathogenesis significantly increased when Rituximab, a chimeric antibody directed against the B cell marker CD20, was initiated in RA with marked clinical responses (4). As CD20 is highly expressed on the surface of pre-B lymphocytes as well as on both resting and activated mature B cells it is still unclear whether the major clinical response is induced by affecting mature B or pre-B cells (5).

CASE REPORT

We describe a 50 year old male with congenital agammaglobulinemia, who developed a classical erosive RA. The patient initially presented to our rheumatology clinic with a recurrent bilateral synovitis of the knees and wrists from which he had been suffering for more than a year. He had a medical history of recurrent respiratory tract infections due to a congenital agammaglobulinemia, for which he received intravenous gammaglobulin treatment. All immunoglobulin subclass levels in serum were found to be below the detection limit. Likewise, rheumatoid factor and other RA associated autoantibodies were found to be negative and remained undetectable throughout the entire medical history of this patient. Concordantly, a profound deficiency in circulating B cells (< 0.1%) as well as in the bone marrow was observed in this patient with virtually no plasma cells. The genetic defect underlying B cell development was subsequently analysed. Approximately 85% of patients affected with a congenital B cell deficiency are males with a mutation in the X-chromosome-encoded cytoplasmic Bruton’s tyrosine kinase (Btk). In search for such mutations we first examined exon 15 of the Btk gene by genomic PCR using exon spanning primers, as this gene most frequently carries mutations in X-linked agammaglobulinemia (XLA) (6). Interestingly, a deletion of the entire exon 15 was
observed in the genome of this patient (Fig 1.A upper panel). However, not the entire Btk gene was affected as illustrated by genomic PCR for exon 2 which was found to be intact (Fig 1.B lower panel). These findings indicate that XLA could be genetically confirmed in this patient based on a deletion in exon 15 of the Btk gene. Such deletions have been previously reported in other XLA patients (6).

Additional investigations at the initial visits could not demonstrate joint erosions on X-rays. Repeated cultures and stainings on synovial fluid specimens for bacteria, fungi, mycoplasma, ureaplasma, and mycobacteria were found to be negative. HLA genotyping demonstrated the presence of the RA associated HLA-DRB1*0401 subtype. Adequate substitution of gammaglobulins has been reported to alleviate arthritis associated with hypogammaglobulinemia (7-9). However, in this patient gammaglobulin substitution did not improve the synovitis. On the contrary, articular symptoms progressively deteriorated with additional involvement of metacarpophalangeal and interphalangeal joints. Furthermore, the patient also developed subcutaneous nodules over the extensor sides of the left elbow. Because of local pressure symptoms, a nodule was excised. The histological picture of this nodule was undistinguishable from classical rheumatoid nodules (Fig 2.A and B). To further examine the lymphocyte composition within the synovial tissue and subcutaneous nodules we performed immunohistochemistry for CD3, CD4, CD8, CD68, CD20, kappa and lambda chains (Fig 3). While the synovial lining and the palisading layer in the nodules contain plenty of CD68+ cells, similar as described in RA patients, the lymphocyte composition by contrast was quite unique. In both tissues, the lymphocytic infiltrates were composed almost exclusively of CD8+ T cells, with virtually no CD4+ T cells (Fig 3). For comparison, 83% of the T cells in peripheral blood consisted of CD8+ T cells versus 12% CD4+ T cells. However, there was no evidence for CD20, kappa or light chain expressing cells within either synovial tissue or subcutaneous nodule in this patient. We also generated T cell lines from either synovial tissue or the subcutaneous nodule by IL-2 expansion and observed that, contrary to previous reports in RA patients, these T cell lines were predominantly CD8+ (mean percentage CD8+ T cells: 93,3 ± 5,4).

Because of the profound polyarthritis in a adequately substituted XLA patient, disease modifying antirheumatic drug therapy was installed with methotrexate at a dose of 15 mg/week resulting in moderate clinical improvement. In spite of the clinical response, radiological progression was observed in the carpal and metacarpophalangeal (MCP) joints of both hands (Fig 1.B) leading to joint destruction. In addition, the patient developed a destructive synovitis of the right hip for which he eventually underwent total joint replacement. Histological examination revealed a marked chronic synovitis with synovial hyperplasia (Fig 2.C and D) and formation of a destructive pannus leading to cartilage destruction (Fig 2.E). While the patient’s locomotoric situation remained stable for about 3 years, his general condition however, deteriorated and in 1999 he developed a massive bilateral pneumonia to which he succumbed.

DISCUSSION

For many years it has been known that hypo- and agammaglobulinemia can be accompanied by a symmetrical polyarthritis that clinically resembles RA. Unlike RA, this form of arthritis usually has a benign course, is non-erosive, usually responds well to immunoglobulin replacement therapy and is not accompanied by extra-articular manifestations typical of RA (7-9). Septic arthritis, especially those caused by mycoplasma or ureaplasma infections, may also occur in patients with hypo- and agammaglobulinemia, although we had no evidence for such infections in the case presented here (9). While the existence of a destructive RA like disease has been
described in acquired hypogammaglobulinemia, particularly common variable immunodeficiency, as well as the occurrence of subcutaneous nodules, no such reports exist to date in patients with a congenital agammaglobulinemia, type XLA (10). The patient’s locomotoric symptoms presented here fulfilled all but one (presence of rheumatoid factor) of the ACR classification criteria for RA (11). Furthermore other striking features of RA such as the presence of the HLA-DR4 shared epitope and the histological signs of inflammation with formation of a destructive pannus completed the clinical picture of RA. Altogether, this patient represents the first case of classical RA with extra-articular manifestations in an adult patient with definitive XLA.

To characterize the inflammatory infiltrate we performed a detailed immunohistochemical analysis on synovial tissue and subcutaneous nodule. Lymphocytic infiltrates adjacent to the synovial lining consisted almost exclusively of CD8+ T cells. Likewise, the subcutaneous nodule was characterized by a pallisading layer of CD68+ cells surrounded by lymphocytic aggregates of CD8+ cells. No staining for CD4+ T cells, CD20 or kappa or light chains could be demonstrated in these tissues. These findings are concordant with previously reported excessive suppressor T cell activity in XLA-associated arthritis (12). Other studies have indicated that the lymphocytic infiltrate in synovial tissue of patients with primary hypogammaglobulinemia suffering from polyarthritis may also contain many CD8+ T cells, contrary to RA where CD4+ lymphocytes prevail over CD8+ T cells (8). Our results also illustrate that lymphocytic infiltrates within the subcutaneous nodules in this patient consisted predominantly of CD8+ T cells which is in contrast with the findings in nodules from classical RA (13). By contrast, the fraction of CD8+ T cells, although significantly elevated compared to values reported in healthy controls or RA patients, was lower in the peripheral circulation suggesting that CD8+ T cells were locally expanded within the synovium or nodule. Consistent with this, IL-2 expanded T cell lines from either synovial tissue or subcutaneous nodules were predominantly CD8+. The precise reasons by which CD8+ predominate in XLA associated arthritis remain however unknown.

In view of the renewed interest in the role of RA associated antibodies in the pathogenesis of this disease, it could be postulated that administration of gammaglobulins may have contributed to the pathogenesis in this patient by adoptive transfer of autoantibodies. We consider this however highly unlikely in view of the rigorously controlled production of gammaglobulins and their broad and safe usage in a variety of diseases.

A major dilemma remains how to reconcile XLA and RA in view of the marked effects of B cell directed therapies? XLA is characterized by a severe block in B-cell development at the pre-B-cell stage, the majority of that due to mutations in the Btk gene (6). Several reports have indicated that these patients still have some early human B cell precursors, V-preB+L+ B cells, some of which may be found in RA synovia (14). These are B cells that coexpress surrogate and conventional light chains, and have an antibody repertoire consistent with antiself reactivity and display signs of receptor editing (14). Many years ago, the history of a four year old boy with no detectable gammaglobulins in the circulation suffering from a polyarthritis was reported. Interestingly, within the synovial fluid and tissue of this patient, immunoglobulins could clearly be detected suggestive of locally immunoglobulin secreting B cell subsets (15). Unfortunately, no extensive immunophenotypical analysis could be performed at the time to further characterize these cells. However, in the present case there was no evidence for CD20, kappa or light chain expression within the synovial tissue or within the subcutaneous nodule, which argues against the possibility that B cell subsets such as V-preB+L+ B cells contributed locally to the synovial inflammation or in the formation or maintenance of the subcutaneous nodules.
In summary, this patient’s history demonstrates that a classical RA with erosive polyarthritis and subcutaneous nodules may develop in the absence of mature B cells.
FIGURE LEGENDS

Figure 1: Erosive polyarthritis in a patient with X-linked agammaglobulinemia. A. Genomic PCR for exon 15 and 2 of the human Btk gene in patient RC. Positive (2 healthy volunteers) and negative (no DNA) controls are depicted. B. Radiological progression over a time period of 18 months. X-rays of MCP 2 & 3 joints of the right hand are shown.

Figure 2: Histology of destructive chronic arthritis with pannus formation and subcutaneous nodules (H&E staining). A. Rheumatoid nodule. Central zone of fibrinoid necrosis is surrounded by pallisading layer of epithelioid macrophages (x 64). B. Detail of the epithelioid macrophage layer (x 160). C. Synovial tissue. Proliferation of synovial layer, mononuclear cell infiltration in the subintima and neovascularization (x 64). D. Detail of the synovial layer (x 160). E. Synovial-cartilage junction. Synovial pannus invades and erodes articular cartilage (x160).

Figure 3 : Immunohistochemical analysis of synovial tissue (upper panel) and a subcutaneous nodule (lower panel). Immunoperoxidase staining for CD68, CD4 and CD8 are shown (x 64).
REFERENCES

Figure 1

A

Exon 15

Exon 2

RC  +  +  -

B
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