

CONCISE REPORT

X linked agammaglobulinaemia and rheumatoid arthritis

G Verbruggen, S De Backer, D Deforce, P Demetter, C Cuvelier, E Veys, D Elewaut



Ann Rheum Dis 2005;64:1075–1078. doi: 10.1136/ard.2004.030049

Background: Much interest has been shown recently in the pathogenic role of B cells in rheumatoid arthritis (RA) owing to the marked clinical responses to anti-CD20 treatment in RA.

Case report: A patient with X linked agammaglobulinaemia (XLA) presented with an erosive symmetric polyarthritis with histological features of RA, including formation of a destructive pannus. Furthermore, the patient developed subcutaneous nodules that were histologically indistinguishable from rheumatoid nodules. Surprisingly, lymphocytic infiltrates in both the synovium and nodule consisted almost exclusively of CD8⁺ T cells.

Discussion: Although some peculiar B cell subsets have been described in patients with XLA, 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.

For many years, the role of B cells in the pathogenesis of rheumatoid arthritis (RA) has been debated. Apart from the production of RA associated autoantibodies, such as rheumatoid factor and more recently the anti-citrullinated antibodies, no additional data have suggested that B cells have an important role. 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 patients with RA 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 used 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 man with congenital agammaglobulinaemia, who developed a classical erosive RA. The patient initially presented to our rheumatology clinic with recurrent bilateral synovitis of the knees and wrists which he had had for more than 1 year. He had a medical history of recurrent respiratory tract infections due to congenital agammaglobulinaemia, for which he received intravenous gammaglobulin treatment. All the 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 seen in this patient, with virtually no plasma cells.

The genetic defect underlying B cell development was subsequently analysed. About 85% of patients with a congenital B cell deficiency are men with a mutation in the X chromosome encoded cytoplasmic Bruton's tyrosine kinase (Btk). In a search for such mutations we first examined exon 15 of the Btk gene by genomic polymerase chain reaction (PCR) using exon spanning primers, as this gene most frequently carries mutations in X linked agammaglobulinaemia (XLA).⁶ Interestingly, a deletion of the entire exon 15 was observed in the genome of this patient (fig 1A, upper panel). However, the entire Btk gene was not affected, as illustrated by genomic PCR for exon 2, which was found to be intact (fig 1A, 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 patients with XLA.⁶

Additional investigations at the initial visits could not demonstrate joint erosions on x ray examination. 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 hypogammaglobulinaemia.^{7–9} However, in this patient gammaglobulin substitution did not improve the synovitis. On the contrary, articular symptoms progressively deteriorated, with additional involvement of the metacarpophalangeal (MCP) 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 indistinguishable from classic rheumatoid nodules (figs 2A and B).

To further examine the lymphocyte composition within the synovial tissue and subcutaneous nodules we carried out immunohistochemical investigations for CD3, CD4, CD8, CD68, CD20, κ and λ chains (fig 3). Whereas the synovial lining and the pallisading layer in the nodules contained plenty of CD68⁺ cells, similar to those described in patients with RA, the lymphocyte composition, in contrast, was 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

Abbreviations: Btk, Bruton's tyrosine kinase; GPI, glucose-6-phosphate isomerase; MC, metacarpophalangeal; PCR, polymerase chain reaction; RA, rheumatoid arthritis; XLA, X linked agammaglobulinaemia

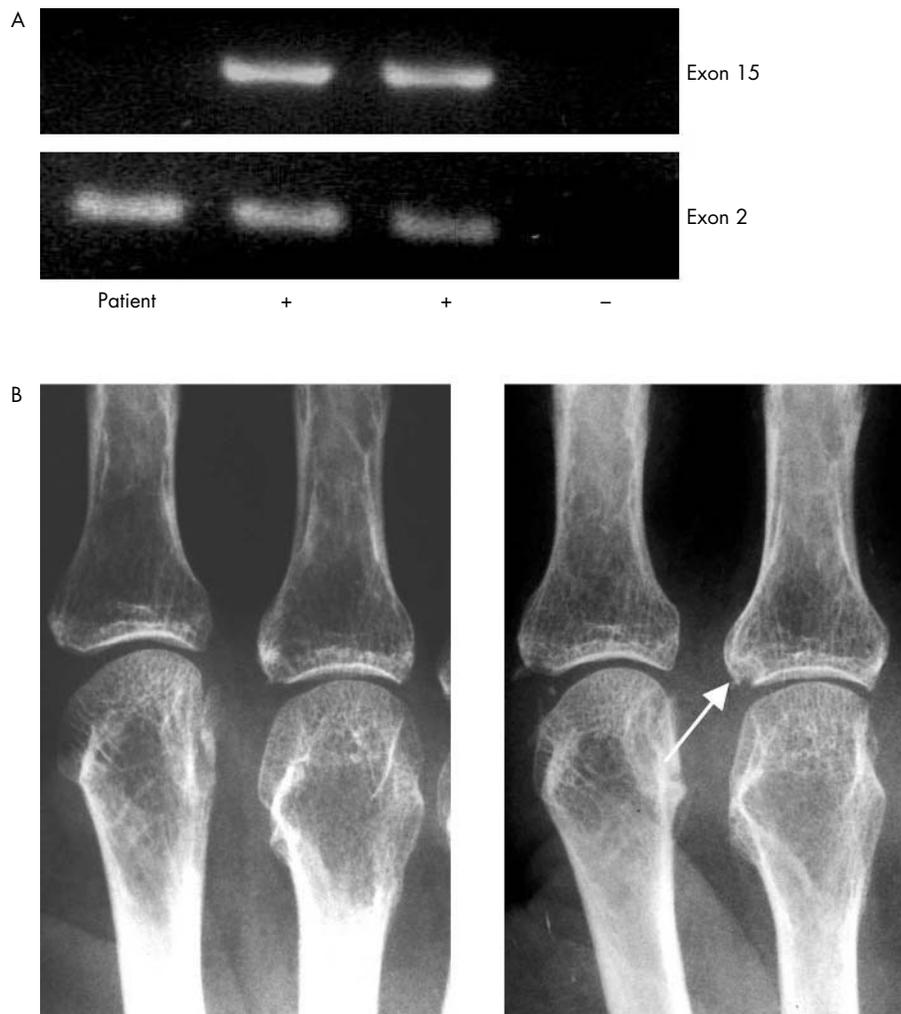


Figure 1 Erosive polyarthritis in a patient with XLA. (A) Genomic PCR for exons 15 and 2 of the human Btk gene in the patient. Positive (two healthy volunteers) and negative (no DNA) controls are depicted. (B) Radiological progression over 18 months. Radiographs of MCP joints 2 and 3 of the right hand.

cells. However, there was no evidence for CD20, κ or light chain expressing cells within either synovial tissue or subcutaneous nodule within this patient. We also generated T cell lines from either synovial tissue or the subcutaneous nodule by interleukin 2 expansion and observed that, contrary to previous reports in patients with RA, these T cell lines were predominantly CD8⁺ (mean (SEM) percentage CD8⁺ T cells 93.3 (5.4)).

Because of the profound polyarthritis in a patient with XLA adequately substituted with gammaglobulins, disease modifying antirheumatic drug treatment was started with methotrexate at a dose of 15 mg/week, resulting in moderate clinical improvement. Despite the clinical response, radiological progression was observed in the carpal and MCP joints of both hands (fig 1B), 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 disclosed a marked chronic synovitis with synovial hyperplasia (figs 2C and D) and formation of a destructive pannus, leading to cartilage destruction (fig 2E). Although the patient's locomotor ability remained stable for about 3 years, his general condition deteriorated, and in 1999 he developed a massive bilateral pneumonia and died.

DISCUSSION

For many years it has been known that hypo- and agammaglobulinaemia can be accompanied by a symmetric 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 treatment, and is not accompanied by extra-articular manifestations typical of RA.⁷⁻⁹ Cases of septic arthritis, especially those caused by mycoplasma or ureaplasma infections, may also occur in patients with hypo- and agammaglobulinaemia, although we had no evidence for such infections in the case presented here.⁹ Although the existence of a destructive RA-like disease has been described in acquired hypogammaglobulinaemia, particularly the common variable immunodeficiency, and the occurrence of subcutaneous nodules, no such reports exist to date in patients with congenital XLA.¹⁰ The patient's locomotor symptoms presented here fulfilled all but one (presence of rheumatoid factor) of the American College of Rheumatology 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

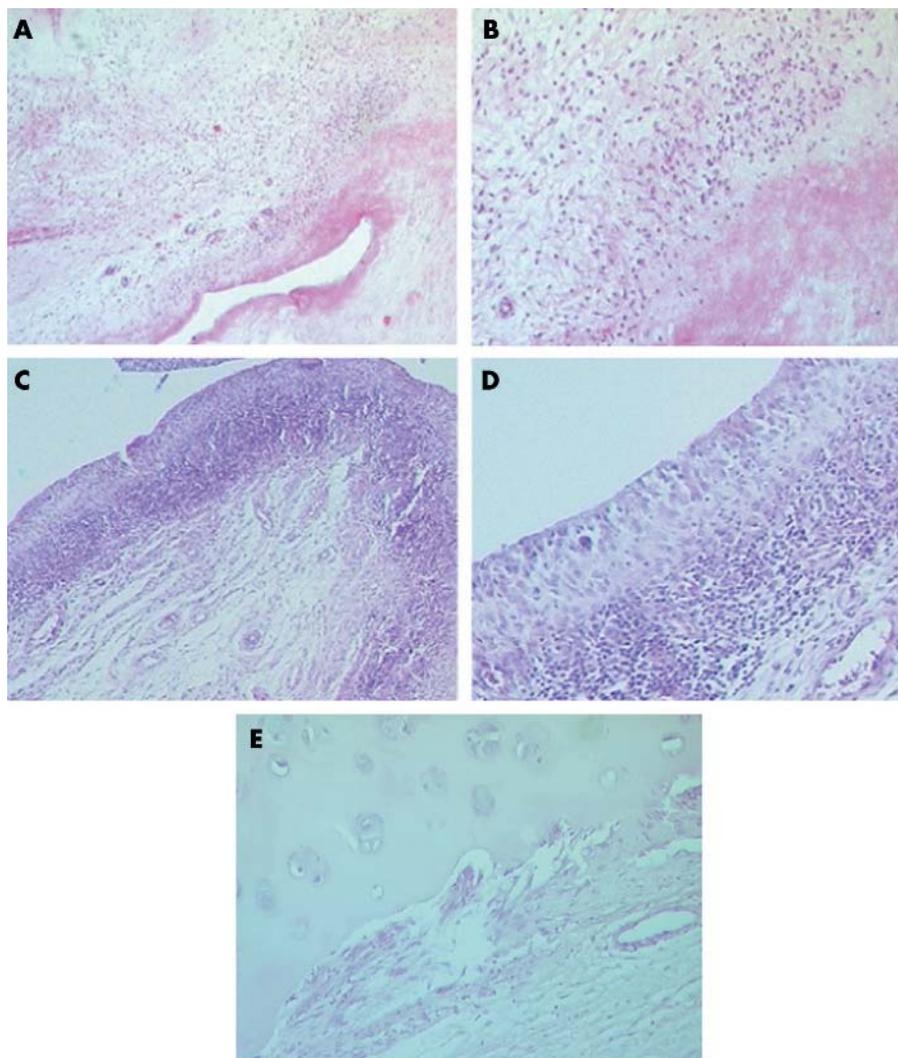


Figure 2 Histology of destructive chronic arthritis with pannus formation and subcutaneous nodules (haematoxylin and eosin staining). (A) Rheumatoid nodule. Central zone of fibrinoid necrosis is surrounded by palisading layer of epithelioid macrophages ($\times 64$). (B) Detail of the epithelioid macrophage layer ($\times 160$). (C) Synovial tissue. Proliferation of synovial layer, mononuclear cell infiltration in the subintima and neovascularisation ($\times 64$). (D) Detail of the synovial layer ($\times 160$). (E) Synovial-cartilage junction. Synovial pannus invades and erodes articular cartilage ($\times 160$).

of classical RA with extra-articular manifestations in an adult patient with definitive XLA.

To characterise the inflammatory infiltrate we performed a detailed immunohistochemical analysis on synovial tissue and subcutaneous nodules. Lymphocytic infiltrates adjacent to the synovial lining consisted almost exclusively of $CD8^+$ T cells. Likewise, the subcutaneous nodule was characterised by a palisading layer of $CD68^+$ cells surrounded by lymphocytic aggregates of $CD8^+$ cells. No staining for $CD4^+$ T cells, $CD20$ or κ 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 hypogammaglobulinaemia with polyarthritis may also contain many $CD8^+$ T cells, in contrast with 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 increased compared with values reported in healthy controls or patients

with RA, was lower in the peripheral circulation, suggesting that $CD8^+$ T cells were locally expanded within the synovium or nodule. Consistent with this, interleukin 2 expanded T cell lines from either synovial tissue or subcutaneous nodules were predominantly $CD8^+$. The precise reasons for the predominance of $CD8^+$ in XLA associated arthritis, however, remain unknown.

In view of the renewed interest in the role of RA associated antibodies in the pathogenesis of this disease, it might be postulated that administration of gammaglobulins contributed to the pathogenesis in this patient by adoptive transfer of autoantibodies. We consider this highly unlikely, however, 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 treatments. XLA is characterised by a severe block in B cell development at the pre-B cell stage, most of which is due to mutations in the Btk gene.⁶ Several reports have indicated that these patients still have some early human B cell precursors, V-pre- B^+L^+ B cells, some of which may be found in RA synovia.¹⁴ These are B cells that coexpress surrogate and conventional light chains,

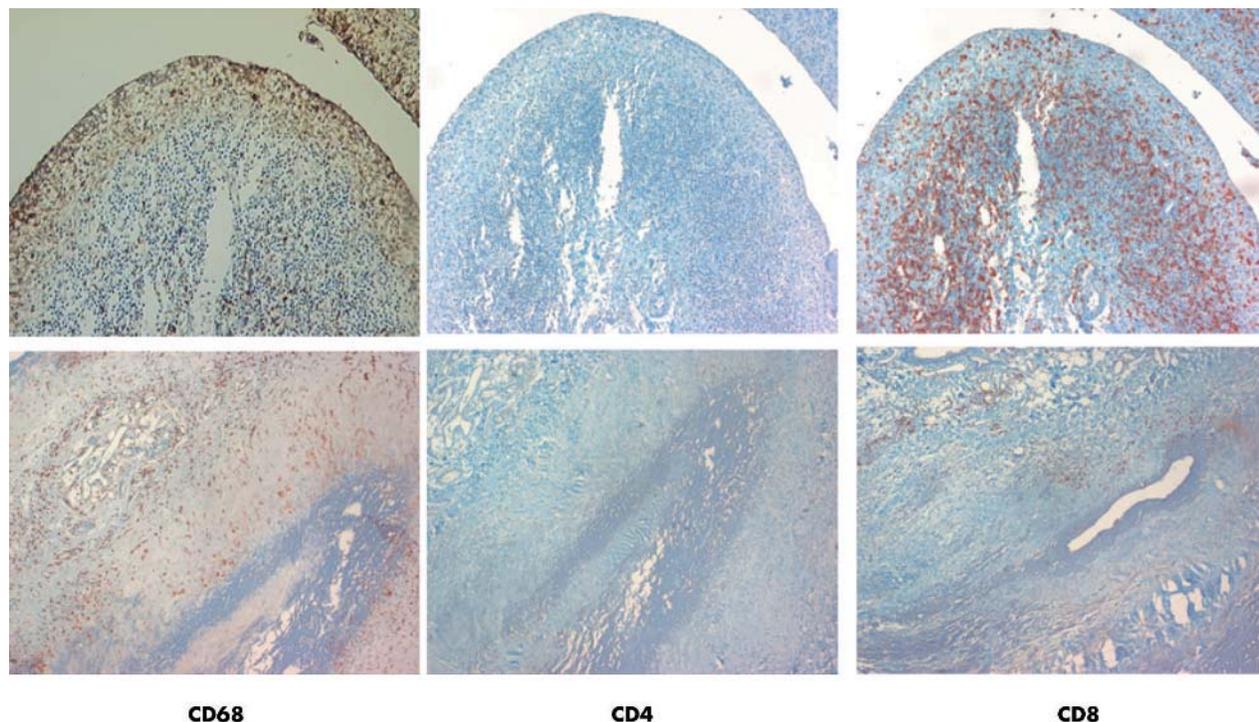


Figure 3 Immunohistochemical analysis of synovial tissue (upper panel) and a subcutaneous nodule (lower panel). Immunoperoxidase staining for CD68, CD4, and CD8 are shown ($\times 64$).

and have an antibody repertoire consistent with antiself reactivity, and display signs of receptor editing.¹⁴

Many years ago, the history of a 4 year old boy with no detectable gammaglobulins in the circulation with a polyarthritis was reported. Interestingly, within the synovial fluid and tissue of this patient, immunoglobulins could clearly be detected, suggestive of local immunoglobulin secreting B cell subsets.¹⁵ Unfortunately, no extensive immunophenotypical analysis could be performed at the time to characterise these cells further. However, in the present case there was no evidence for CD20, κ 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-pre-B⁺L⁺ B cells contributed locally to the synovial inflammation or to 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.

Authors' affiliations

G Verbruggen, E Veys, D Elewaut, Department of Rheumatology, University Hospital Gent, Belgium

S De Backer, D Deforce, Laboratory of Pharmaceutical Biotechnology, University of Gent, Belgium

P Demetter, C Cuvelier, Department of Pathology, University of Gent, Belgium

*GV and SDB contributed equally to this manuscript.

Correspondence to: Assistant Professor D Elewaut, Department of Rheumatology, University Hospital Gent, De Pintelaan 185, 9000 Gent, Belgium; dirk.elewaut@ugent.be

Accepted 21 November 2004

Published Online First 25 November 2004

REFERENCES

- Muller-Ladner U, Kriegsmann J, Franklin BN, Matsumoto S, Geiler T, Gay RE, et al. Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. *Am J Pathol* 1996;**149**:1607–15.
- Matsumoto I, Staub A, Benoist C, Mathis D. Arthritis provoked by linked T and B cell recognition of a glycolytic enzyme. *Science* 1999;**286**:1732–5.
- Matsumoto I, Lee DM, Goldbach-Mansky R, Sumida T, Hitchon CA, Schur PH, et al. Low prevalence of antibodies to glucose-6-phosphate isomerase in patients with rheumatoid arthritis and a spectrum of other chronic autoimmune disorders. *Arthritis Rheum* 2003;**48**:944–54.
- Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
- Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. *Arthritis Rheum* 2003;**48**:1484–92.
- Vihinen M, Brandau O, Branden LJ, Kwan SP, Lappalainen I, Lester T, et al. BTKbase, mutation database for X-linked agammaglobulinemia (XLA). *Nucleic Acids Res* 1998;**26**:242–7.
- Sany J, Jorgensen CH, Anaya JM, Didry C, Andary M, Serre I, et al. Arthritis associated with primary agammaglobulinemia: new clues to its immunopathology. *Clin Exp Rheumatol* 1993;**1**:65–9.
- Pipitone N, Jolliffe VA, Cauli A, Scott DG, Pitzalis C. Do B cells influence disease progression in chronic synovitis? Lessons from primary hypogammaglobulinaemia. *Rheumatology (Oxford)* 2000;**39**:1280–5.
- Lee AH, Levinson AI, Schumacher HR. Hypogammaglobulinemia and rheumatic disease. *Semin Arthritis Rheum* 1993;**22**:252–64.
- Hermaszewski R, Ratnavel R, Webster ADB, Denman AM. Rheumatoid arthritis in a patient with primary hypogammaglobulinemia. *Br J Rheumatol* 1993;**32**:636–9.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- Chattopadhyay C, Natvig JB, Chattopadhyay H. Excessive suppressor T-cell activity of the rheumatoid synovial tissue in X-linked hypogammaglobulinaemia. *Scand J Immunol* 1980;**11**:455–9.
- De Keyser F, Verbruggen G, Veys EM, Cuvelier C, Malfait AM, Benoist D, et al. T cell receptor V β usage in rheumatoid nodules: marked oligoclonality among IL-2 expanded lymphocytes. *Clin Immunol Immunopathol* 1993;**68**:29–34.
- Meffre E, Davis E, Schiff C, Cunningham-Rundles C, Ivashkiv LB, Staudt LM, et al. Circulating human B cells that express surrogate light chains and edited receptors. *Nat Immunol* 2000;**1**:207–13.
- Barnett EV, Winkelstein A, Weinberger HJ. Agammaglobulinemia with polyarthritis and subcutaneous nodules. *Am J Med* 1970;**48**:40–7.