Collins (1966) mentioned changes of an inflammatory character causing joint enlargement. Our patient had definite recurrent synovial effusions, but the cytology proved that this was not an inflammatory fluid. Synovial biopsy also revealed an absence of cellular infiltration and only minimal synovial cell hyperplasia. Thus, in this case, in spite of effusions in multiple joints, there was no pathological evidence of inflammatory arthritis. It is possible that the effusion was an oversecretion due to the increased vascularity of the synovium where it is in contact with the underlying hypervascular periostuem.

Acknowledgments

We wish to thank Dr C. Tribe for his help with the pathology, Mr E. F. J. Ring for his skilled technical assistance with thermographic examinations, and Winthrop Laboratories for their support in purchasing the thermographic apparatus. G. R. was in receipt of a grant from the Arthritis and Rheumatism Council.

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Progressive systemic sclerosis and autoimmune haemolytic anaemia

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Summary

The development of progressive systemic sclerosis (PSS) in a patient with established autoimmune haemolytic anaemia is described. Points favouring an immunological aetiology for PSS are reviewed and discussed.

Since the first report by Fundenberg and Wintrobe (1955) describing the association between progressive systemic sclerosis (PSS) and autoimmune haemolytic anaemia, other similar cases have been reported (Steiner, Haeger-Aronsen and Nielsen, 1967; Westerman et al., 1968; Chaves et al., 1970; Ivey et al., 1971; Rosenthal and Sack, 1971). All reported cases presented initially with features of PSS and were only later complicated by autoimmune haemolytic anaemia. In 1973, Loft and Olsen described a case which presented with autoimmune haemolytic anaemia but had on examination features of PSS as well. In none of the previously reported cases had autoimmune haemolytic anaemia preceded the development of PSS.

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Case report

A 24-year-old Chinese female first presented with jaundice and anaemia and was treated symptomatically by a private doctor. She was not fully investigated at that time. A second episode of jaundice and anaemia occurred 15 months later, when she was admitted to the University Hospital, Kuala Lumpur, with exertional dyspnoea, malaise and lethargy. Physical examination revealed her to be clinically anaemic and mildly icteric. The skin appeared normal. Cardiac and pulmonary findings were normal. The liver was not enlarged but the spleen was palpable 2 cm below the costal margin. Laboratory investigations revealed Hb 7·2 g/100 ml; MCHC 30%; reticulocytes 10·2%; WBC 4900/μl (neutrophils 89%, lymphocytes 6%, monocytes 3%, eosinophils 2%); platelet count 212,000/μl. The ESR (Westergren) was 122 mm/hr. The urine contained urobilinogen but not bilirubin. Serum total bilirubin was 2·9 mg/100 ml and unconjugated bilirubin 2·6 mg/ml. The direct Coombs’ test was repeatedly positive. The direct Coombs’ test positive red cells gave eluates which reacted with papain sensitized red cells maximally at 4°C. Plasma protein electrophoresis showed raised θ-globulins. Immuno-electrophoresis showed an increase in IgM. The red blood cells showed autoagglutination as well as rouleaux formation at 4°C. The cold agglutinins in the serum showed no demonstrable specificity. Repeated examinations for LE cells, antinuclear antibody and rheumatoid factor were all negative. The Donath-Landsteiner and VDRL tests were also negative. A diagnosis of autoimmune haemolytic anaemia was made. Treatment with prednisolone 60 mg/day was commenced with fairly good response. The haemolysis was controlled and the ESR became normal. She was maintained on prednisolone 10 mg/day and regularly followed-up at the Haematology Clinic.

Two years later she first complained that her fingertips became blue and painful on exposure to the cold. The skin over her fingertips was noted to be pale. Further observation confirmed Raynaud’s phenomenon.

Six months later, she was found to have thickening of the skin of the fingers of both hands. PSS was suspected and confirmed by skin biopsy.

Within a year, the skin of both forearms had become involved and there was some loss of mobility of facial skin. She also developed dysphagia but barium studies to demonstrate oesophageal involvement were deferred because the patient was pregnant at that time.

Discussion

This case report describes the development of PSS in a patient with established autoimmune haemolytic anaemia.

Despite numerous theories concerning aetiology and pathogenesis, the fundamental nature of PSS remains obscure. However, the demonstration of several immunological abnormalities in PSS (Rothfield and Rodnan, 1968), together with the association of PSS with disorders of known immunological origin, has strengthened the view that aberrant immunity may be important in pathogenesis.

In PSS, inflammatory and vascular lesions resembling those seen in other immunologically connective tissue diseases have been described. Inflammation is present most frequently in the form of synovitis, and synovial biopsy examination early in the course of the disease has revealed an inflammatory reaction characterized by the infiltration of lymphocytes, plasma cells and smaller numbers of polymorphs. The appearance of the synovium at this time is not unlike that observed in milder cases of rheumatoid arthritis (Rodnan, 1963). Vascular changes may occur in the small vessels of the lungs, heart, gastrointestinal tract, striated muscle and kidneys of patients with PSS (Rodnan, 1963). The renal vascular lesions consist of intimal hyperplasia of the interlobular arteries and fibrinoid necrosis of afferent arterioles and glomerular tufts. Schafer and Schafer (1968) found that 7S γ-globulin may occur in the fibrinoid material in the kidneys, while McGiven, deBoer and Barnett (1971) demonstrated collections of immunoglobulins (predominantly IgM) and complement in the basement membranes in the subendothelial region of glomeruli of patients with PSS. β1c Globulin deposition was found by Stone et al. (1974) in the mesangium and tubular basement membranes of their patient with PSS complicated by acute renal failure.

Hypergammaglobulinaemia occurs in about 50% of patients with PSS (Rodnan, 1963). The increase usually involves IgG; less often elevations of IgA and IgM (Rothfield and Rodnan, 1968). Between 25% and 33% of patients with PSS have positive tests for rheumatoid factor, and antinuclear antibodies are demonstrable in 75% or more patients (Rothfield and Rodnan, 1968). Positive LE cell reactions and false positive serological reactions for syphilis have been recorded (Rodnan, 1963).

A picture similar to PSS has been produced in rats by the injection of homologous lymphocytes into a recipient which had previously been made tolerant to these cells (Stasny, Stembridge and Ziff, 1963). The fact that PSS can be produced in experimental animals by the injection of immunologically active cells which react against the recipient but cannot be rejected, suggests an immunological mechanism.
in this disease (Turk, 1972). Thymic changes have also been noted in PSS. Biggert and Nevin (1967) described the thymus in PSS as hyperplastic with numerous Hassall’s corpuscles, medullary lymphoid follicles and plasma cells, features interpreted as evidence of disturbed immunological function. Lymphocyte toxicity to muscle, fibroblasts and epithelial cells has been described in PSS (Currie, Saunders and Knowles, 1971) and, using the leucocyte migration tests, Hughes, Holt and Rowell (1974) have demonstrated widespread cell-mediated hypersensitivity in PSS to human tissue antigens.

An indirect but strong argument favouring immunopathogenesis is the contribution of PSS to the ‘overlap syndromes’. PSS has been associated with rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren’s syndrome, dermatomyositis, Hashimoto’s thyroiditis and hypogammaglobulinaemia (Miescher and Muller-Eberhard, 1969). In ‘mixed connective tissue disease’, patients may present with features of PSS and clinical and serological features highly suggestive of SLE, and often exhibit a specific antibody to an extractable nuclear antigen (Sharp et al., 1971). PSS has also been reported in association with primary biliary cirrhosis (Reynolds et al., 1971) and it has been suggested that this association may be due to a common autoimmune process (Murray-Lyon et al., 1970).

Haemolytic anaemia has been described as the first symptom in periarteritis nodosa (PAN) and as a chronic complication of PAN (Dameshek and Rosenthal, 1951; Lovshin, 1952). Autoimmune haemolytic anaemia is well documented as a feature of SLE and has been known to follow or precede other symptoms of SLE by a number of years (Dubois, 1952). The same may occur in PSS. There are now at least eight reported cases of PSS associated with autoimmune haemolytic anaemia; an association which together with other immune phenomena supports a basic immunological disorder. This case demonstrates that autoimmune haemolytic anaemia may be the first symptom of PSS and may precede Raynaud’s phenomenon and skin changes of PSS by a number of years.

Acknowledgments

I wish to thank Associate Professor H. O. Wong and Professor K. S. Lau for permission to publish this case, and Associate Professor J. C. White for the haematological investigations. I am grateful to Dr A. L. Vaterlows and Professor R. A. B. Drury for their encouragement and advice.

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