ACQUIRED HAEMOPHILIA AND RHEUMATOID ARTHRITIS

CASE REPORT

BY R. M. G. SORIANO, J. M. MATTHEWS AND E. GUERADO-PARRA

1Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, University of Oxford, Windmill Road, Headington, Oxford OX3 7LD and 2Oxford Haemophilia Centre, Churchill Hospital, Headington, Oxford, UK

SUMMARY

Four patients with classical rheumatoid arthritis who developed acquired haemophilia are described. They developed a spontaneous bleeding diathesis and diagnosis was based on low or absent Factor VIII levels and the presence of a circulating anticoagulant directed against Factor VIII. The course is variable and cyclophosphamide together with control of the underlying rheumatoid arthritis are recommended as treatment.

KEY WORDS: Acquired haemophilia, Rheumatoid arthritis, Factor VIII antibodies.

ACQUIRED haemophilia is a rare blood coagulation disorder characterized by the development of circulating antibodies to Factor VIII procoagulant activity. These substances are endogenously produced and are of the IgG class possessing both kappa and lambda chains [1].

The first case of acquired haemophilia was reported by Lozner et al. [2] in 1940 and was generally recognized as a disease entity in 1950 when Deutsch published a monograph entitled Hemmkorper Hamophile [3]. Margolius et al. reported on 40 cases in 1961 [4] and by 1975, there were at least 100 cases of acquired haemophilia on record [5]. Circulating antibodies to Factor VIII are found most frequently in patients with severe haemophilia, 7–40% of whom in different series have been found to develop antibodies as a result of repeated administration of Factor VIII-containing material [4, 6]. Spontaneous development of Factor VIII antibodies has been described in association with an established or presumed immunological condition, e.g. rheumatoid arthritis (RA), systemic lupus erythematosus, bronchial asthma and regional enteritis [4, 7, 8]. Other associated conditions include drug allergies, especially penicillin and certain skin diseases, e.g. pemphigus, bullous dermatitis and psoriasis [9, 10]. It has also been reported to occur in previously healthy young women following childbirth and in middle-aged and elderly patients in otherwise good health [4, 11].

This paper reports four cases of classical RA whose Factor VIII antibody was documented and managed at the Oxford Haemophilia Centre, Churchill Hospital.

MATERIALS AND METHODS

Factor VIII was assayed by the two-stage method of Denson and the two-stage assay of Factor VIII antibody was performed according to the method of Biggs and Bidwell [12] or the method of Rizza and Biggs [13].

CASE REPORTS

Case 1

A 57-year-old man with a 9-year history of RA being treated with prednisone was well until October 1965 when he developed spontaneous bleeding at the back of his right knee and into his calf muscles. Factor VIII assay was 0% and his Factor VIII antibody was noted to be 17 units/ml. He was managed with blood and plasma transfusions and his right lower extremity was immobilized in a plaster of Paris back slab. Treatment with prednisone was continued and he was discharged apparently improved 3 months later.

He then had several bleeding episodes which were managed at home. A year later, he developed a huge right shoulder bleed and an acute myocardial infarction from which he succumbed a day later. The post-mortem report showed areas of infarction and fibrosis of the left ventricle and changes of RA peripherally.

Case 2

A 61-year-old female with rheumatoid arthritis for the previous 18 years and who was on prednisone was well until July 1968 when she had haematemesis and...
melaena. Factor VIII was measured and found to be 0% and a Factor VIII inhibitor was present at more than 3 units/ml. She was treated with azathioprine 100 mg twice daily and prednisone. The patient recovered completely but died 3 years later as a result of an accident.

Case 3

A 59-year-old female with seropositive RA treated with intermittent steroids developed anaemia with purpura and had occult blood in the stools in October 1968. There was no previous history of any bleeding tendency. Physical examination revealed anaemia and mild changes of RA were present in her hands and knees.

Laboratory examination showed a Factor VIII assay of less than 1% and a circulating antibody against Factor VIII. The patient continued to bleed from the gastrointestinal tract and required repeated transfusions. A course of azathioprine 50 mg twice daily resulted in a slight improvement of her condition and a lowering of her inhibitor level.

Two months later, she was readmitted with what appeared to be an infected haematoma of her leg. This was treated with porcine Factor VIII to which she responded, but 3 days later, she went into renal failure, bled uncontrollably from the gut despite a high level of Factor VIII and died. Necropsy showed acute tubular necrosis, haemorrhagic colitis, bilateral phlebothrombosis and an infected haematoma of the right calf muscle. Changes of RA and recent septicaemia were found but no evidence of renal vein thrombosis.

Case 4

A 71-year-old male was seen in January 1981 because of severe bruising following a relatively trivial injury. He had a long history of RA with a high DAT titre and a strongly positive latex test. Factor VIII assay was 0% and Factor VIII antibody was 185 Oxford new units/ml. He was treated with cyclophosphamide 100 mg daily with dramatic improvement in his condition. The Factor VIII antibody level progressively declined until 1 year later it could no longer be detected and his Factor VIII level had gone up to 28%.

DISCUSSION

The association of RA with circulating antibodies to Factor VIII is rare. Out of a total of 26 patients with acquired haemophilia seen at the Oxford Haemophilia Centre over a 23-year period (1963–86), only four cases have been documented as having RA. A review of the world literature shows only 14 case reports of such a condition, although Green et al. [7] suggested that this association may occur far more frequently but may have been described only in those patients whose outcome has been favourably influenced by therapy.

All the patients in this series were elderly (mean age 62 years) and except for the RA were in good health. The presenting complaint was a serious bleeding disorder of spontaneous onset. Laboratory examination revealed absent or markedly decreased Factor VIII and the presence of a circulating antibody to Factor VIII.

Nilsson and Lamme [14] reported that the inhibitors to Factor VIII in non-haemophiliacs have always been gammaglobulins (IgG) which are not monoclonal (7S). The spontaneous inhibitors have both kappa and lambda light chains in contrast to those found in congenital haemophilia which only have one light chain, usually kappa [15].

The exact mechanism for the production of Factor VIII antibodies in patients with RA remains unknown. It seems likely that the occurrence of acquired circulating Factor VIII antibodies is related to an autoimmune phenomenon [5, 11].

Various forms of treatment have been suggested but, because Factor VIII inhibitors may disappear spontaneously, it has been difficult to evaluate the therapeutic effects of any treatment regimen. Corticosteroids, antimetabolites and alkylating agents have been given singly or in combination in an attempt to reduce or prevent production of the inhibitor [4, 13, 14]. The successful treatment of 11 non-haemophilic patients, including three patients with RA, with cyclophosphamide alone or in combination with Factor VIII and prednisone has recently been described [7]. In our series, the three earlier patients were treated initially with prednisone and two of them later with azathioprine with relatively poor results. The use of cyclophosphamide in the last patient resulted in a significantly better result and this would appear to be the immunosuppressive of choice for such a condition.

The progress of the bleeding disorder seems to be largely associated with the activity of the associated disease and in some cases the antibody disappears after the underlying disease is cured [17]. It is therefore important to attempt control of the underlying RA while treating the acquired haemophilia.

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