Unusual haematological alterations in rheumatoid arthritis

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ABSTRACT

Three cases of rheumatoid arthritis (RA), presenting with refractory anaemia, thrombocytopenia and peripheral lymphocytosis respectively, were observed. In all the cases haematological manifestations were unrelated to disease activity or drug toxicity. These patients were detected to have pure red cell aplasia (PRCA) (normochromic normocytic anaemia, reticulocytopenia and absence of erythroid precursors in the bone marrow), immune thrombocytopenia (IT) (absence of splenomegaly and presence of increased megakaryocytes in the bone marrow) and multiple myeloma (MM) (lytic lesions on skull, paraproteinaemia and bone marrow plasmacytosis) respectively. PRCA and IT responded to glucocorticoids. Association with these three haematological alterations has rarely been reported. Our report highlights the need to regularly monitor blood counts in patients with RA.

KEY WORDS: Pure red cell aplasia, immune thrombocytopenia, multiple myeloma, refractory anaemia, lymphocytosis

Patients with rheumatoid arthritis (RA) may present with haematological abnormalities either at the time of diagnosis, or during the course of their illness. Anaemia, thrombocytosis and eosinophilia are observed commonly whereas neutropenia, thrombocytopenia, large granular lymphocytosis (LGL) and malignancies are uncommon. We describe three rare haematological disorders, namely pure red cell aplasia (PRCA), immune thrombocytopenia (IT) and multiple myeloma (MM).

Case Histories

Case 1
A 48-year-old female presented with anaemia of 3 months duration. She had seropositive RA for 6 years and was receiving sulfasalazine (SSZ, 1 gram) and indomethacin (100 mg) daily for 12 months. During this period her haemoglobin (Hb), total (TLC) and differential leucocyte counts (DLC) and platelet counts, done 3 monthly, remained normal. Examination confirmed severe anaemia, basal crepitations, hepatomegaly and tender joint count (TJC) of 14 without any swollen or deformed joints. The rest of the examination was unremarkable. Investigations revealed Hb 3.6 g/dl, normochromic red blood cells, corrected reticulocyte count 0.3%, and erythrocyte sedimentation rate (ESR) 80 mm. Haemogram, liver and renal function tests, Coombs test, serology for antinuclear antibody (ANA), HIV-1 and HIV-2, X-ray chest and urinalysis were normal. Stool for occult blood was negative. X-ray hands showed juxta-articular osteopenia (JAO). SSZ was discontinued and three units of packed red blood cells were transfused. She remained transfusion-dependent despite treatment with oral iron, folic acid and parenteral vitamin B12. Bone marrow (BM) examination 3 months later revealed absence of erythroid precursors without other abnormalities, confirming the diagnosis of pure red cell aplasia (PRCA). Anaemia improved with prednisolone (1 mg/kg/day).

Case 2
A 65-year-old female presented with deforming RA of 40 years duration. She received glucocorticoids for the entire period and denied use of disease-modifying anti-rheumatic drug (DMARD) ever. Examination showed deformities of hands and fingers with restricted movements at wrists, knees and elbows. The spine was diffusely tender. The rest of the examination was unremarkable. Investigations revealed TLC 13,900, lymphocytes 66%, ESR 50 mm and Hb 8.4 gm/dl. Urinalysis, renal and liver function tests, serum calcium, phosphorus, protein and albumin were normal. Test for RF was negative.

Case 3
A 52-year-old male presented with symmetric, inflammatory polyarthritis of 3 months duration. The patient was Steinbroker functional Class III (activities restricted, required assistance) and had early morning stiffness (EMS) of >6 hours. There was no history to suggest Sjogren's syndrome, systemic lupus erythematosus or inflammatory myositis. Examination revealed TJC of 18, swollen joint count of 10 and left-sided carpal tunnel syndrome. The rest of the examination was unremarkable. Investigations revealed ESR 40 mm and platelet count 47,000/µl. Haemogram, renal and liver function tests, serum vitamin B12 and folate levels and urinalysis were normal. Rheumatoid factor (RF) was positive. X-ray hands showed soft tissue swelling and JAO at metacarpophalangeal (MCP) and proximal-interphalangeal (PIP) joints. Ultrasonogram of the abdomen was normal. Serology for ANA, anticyclic citrullinated peptide (ACCP), lupus anticoagulant, anti Ro and HIV-1 and HIV-2 was negative. BM examination revealed increased megakaryocytes. Platelet count normalized with prednisolone (1 mg/kg/day).
ANA was positive (2+, diffuse at 1: 40). Serum immunoglobulin, IgG, IgM and IgA were 308 mg/dl (normal 800-1500), 30 mg/dl (normal 45-150) and 795 mg/dl (normal 90-325) respectively. Radiologically, there were erosions and deformities of the hands and knees, atlanto-axial subluxation, generalized osteopenia and lytic lesions in the skull. Immunoelectrophoresis of serum revealed IgA-λ monoclonal protein. Threphine biopsy of the BM showed 18% plasma cells with increased lymphocytes. She is presently receiving melphalan and prednisolone.

**Discussion**

All the three patients fulfilled the American College of Rheumatologist 1987 criteria for the diagnosis of RA.1

Case 1 highlights a distinctly rare cause of anaemia i.e. PRCA.2 Drugs (fenoprofen, D- penicillamine, azathioprine, indomethacin and SSZ).3-5 Parvovirus B19 infection or RA are known to cause PRCA.3 The possibility of Parvovirus B19-induced PRCA was however less likely in our patient as she was immunocompetent. Yet, in the absence of serological workup it cannot be excluded. Insidious onset of anaemia following 1 year of therapy with SSZ and indomethacin, which did not remit after withdrawal of the drugs, favours PRCA due to RA in our patient.3 PRCA may represent an extra-articular manifestation of RA.3 PRCA occurs due to maturation arrest of erythroid precursors by IgG inhibitor,3 natural killer cell or CD 4+ T-cell dysfunction,5 or due to lyses of precursors by LGL.6 Expansion of LGL has been reported in RA.1 Glucocorticoids, cytotoxic agents and immunosuppressive drugs have been tried in the management of PRCA with variable success.3

Immune thrombocytopenia in RA is extremely unusual as exemplified by Case 2. He had IT at the onset of RA, which is in contrast to earlier reports.7,8 There are studies in favour,3 and against,7 the association between IT and disease activity in RA. Both the diseases share a common immunological profile.7,9 The use of non-steroidal anti-inflammatory drugs and DMARDs carry the risk of worsening of thrombocytopenia and bleeding. However, IT in RA is responsive to glucocorticoids, immunosuppressive agents or danazol.7,8

There is an increased risk of malignancy (Hodgkin’s disease, non-Hodgkin lymphoma, leukaemia and MM) in RA independent of immunosuppressive therapy.1,10 As in Case 3, IgA-λ light chain MM is reported more frequently,11 however, MM of other immunoglobulin isotypes may occur.12 Increased exposure to radiation may predispose to MM.10

Haematological manifestations in RA can be broadly categorized into areas of; anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, and haematological malignancies.13 Anaemia in RA is multifactorial—disease activity, drug-induced, nutritional, gastrointestinal bleed, BM suppression, and ineffective erythropoiesis.1 Autoimmune haemolytic anaemia and PRCA are rare. Neutropenia is generally drug-induced or due to Felty’s or T-cell LGL syndrome.14 Thrombocytopenia in RA is usually drug-induced or due to Felty’s syndrome.1 IT is extremely rare.15 Thrombocytosis is related to disease activity. Eosinophilia in RA reflects active disease or hypersensitivity to drugs. Patients with RA and secondary Sjogren’s syndrome may be predisposed to developing MALT lymphoma.17

Since all the haematological alterations discussed above are rare associations with RA, a possibility of chance phenomenon cannot be discounted.

**References**