Pure Red Cell Aplasia Secondary to Rheumatoid Arthritis

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Abstract

Background

Rheumatoid arthritis (RA) is a common autoimmune disease with many extra-articular manifestations. Pure red cell aplasia (PRCA) is a rare manifestation of RA and is sparsely documented in the literature with a variable clinical outcome following immunosuppressive therapy.

Case presentation

A 63-year-old female presented with transfusion-dependent anaemia associated with deforming inflammatory arthritis, who also had leukopenia, right subclavian venous thrombosis, and generalized lymphadenopathy. The diagnosis of RA following initial clinical workup and additional blood and bone marrow investigations revealed PRCA as a secondary manifestation of RA after excluding other secondary causes, such as infections, thymoma, thrombophilic conditions and haematological malignancy. She responded well to oral prednisolone, cyclosporine A and hydroxychloroquine, where she attained complete recovery in two months.

Conclusion

PRCA is a disabling illness that may lead to transfusion-dependent anaemia, which may occur due to rare extrapulmonary manifestation of RA. The diagnosis of PRCA secondary to RA may be challenging where haematological investigations, including bone marrow biopsy, will aid in the diagnosis, and early diagnosis and treatment will bring about a better outcome.

Background

Rheumatoid arthritis (RA) is a common immune-mediated, chronic, symmetrical, inflammatory disease that initially affects small joints, progressing to larger joints and eventually causing extra-articular manifestations involving the skin, eyes, heart, kidneys, and lungs [1, 2]. Pure red cell aplasia (PRCA) is a rare manifestation of RA, a hemopoietic disorder first reported in 1922, presented with normocytic normochromic anaemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow [3, 4]. The clinical outcome of PRCA is variable from complete remission to fatal, and it depends upon the cause and the types of treatment [11]. Therefore, it imposes a diagnostic and therapeutic challenge when PRCA presented with immune-mediated peripheral cytopenias secondary to autoimmune diseases. We present a rare case of PRCA secondary to RA presented with bicytopenia where the patient attained complete recovery with immunosuppressive therapy.

Case Presentation

A 63-year-old female was admitted to the Teaching Hospital Peradeniya in March 2017 with progressive generalized malaise, fatigue and shortness of breath on exertion for a one-week duration. She did not

complain of orthopnoea, paroxysmal nocturnal dyspnoea, or any previous syncopal attacks. There was no history of tingling sensations of the extremities, recurrent infections, previous miscarriages, or any history suggestive of thrombotic episodes.

She also had a seven-year history of pain and swelling in multiple joints, starting from the right ankle joint progressing into multiple large joints in a symmetrical pattern associated with morning stiffness, lasted for about four hours a day. Simultaneously, she had developed involvement of the small proximal joints of the bilateral hands for five years. She had taken some over-the-counter medications, including non-steroidal anti-inflammatory drugs (NSAID), some local applications and some native treatments to relieve these symptoms, where she was using them for several years. She worked as a housemaid abroad when she developed joint pains and noticed some deformities also appearing in the hands towards the end of 2016, where she found it challenging to engage in day-to-day activities.

On the current admission, she was severely pale, and there were boutonniere deformities in the left middle, right middle and right ring fingers; however, there was no evidence of active joint inflammation in the form of swelling or erythema in the small joints of the hands (Fig. 1). There were no skin rashes, photosensitivity rashes, tight skin on the fingers or face, any cutaneous bleeding manifestations, oral ulcers or alopecia. Also, she did not have any dependent oedema. Her vital parameters were stable with a pulse rate of 84 beats per minute, blood pressure of 120/80 mmHg, normal jugular venous pressure without any abnormal heart sounds. Other system examinations were unremarkable.

Her initial investigations revealed a haemoglobin (Hb) level of 1.8 g/dL with normal mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC). The white cell count was $2100/\text{mm}^3$ (neutrophils 55% and lymphocytes 35%) with a platelet count of $169000/\text{mm}^3$, and the reticulocyte count was 0.09 % with negative direct and indirect Coomb's tests. The random blood sugar level was 5.7 mmol/L. Other investigations revealed erythrocyte sedimentation rate (ESR) of 55 mm/hour, C-reactive protein (CRP) 31.68 mg/L, aspartate aminotransferase (AST) 115 U/L, alanine aminotransferase (ALT) 98 U/L, total bilirubin 16.4 $\mu\text{mol/L}$, alkaline phosphatase (ALP) 223.8 U/L, gamma-glutamyl transferase (GGT) 79.1 U/L, serum albumin 22.9 g/dL, and albumin/globulin 0.97. The serum creatinine level was 65 $\mu\text{mol/L}$. The blood electrolyte levels were serum sodium 137 mmol/L, potassium 4 mmol/L, magnesium 1.07 mmol/L and corrected calcium 2.4 mmol/L. The electrocardiographic findings, 2D echocardiogram, urinalysis, clotting profile and chest x-ray were normal.

Then, she was further investigated for an aetiology for anaemia, where the blood picture showed bicytopenia (leukopenia and anaemia) with features more in favour of megaloblastic anaemia. Owing to anaemia, she was transfused with 6 pints of RCC until Hb > 10 g/dL. The serum iron level was 268.5 $\mu\text{g/dL}$ (33–199), and the total iron-binding capacity (TIBC) was within the normal range. The bone marrow biopsy showed markedly reduced erythroid lineage with increased granulopoiesis and normal megakaryopoiesis, and there was no evidence of lymphoma, leukaemia, secondary deposit, or granuloma. Based on these findings, a conclusion of PRCA was made, and leukopenia was thought to be immune in origin. She improved with corticosteroids and supportive treatments with iron, vitamin B12

and folic acid inward and was discharged, and in the two-week follow-up, she had no new complaints. Unfortunately, she did not attend any further clinic follow-ups.

Again she got admitted in September 2017 with right upper limb swelling and was found to have right subclavian vein thrombosis. The lower limb venous duplex was typical, and there was no evidence of pulmonary embolism. The anticoagulation was done initially with enoxaparin and warfarin and subsequently continued with warfarin. The thrombophilia screen was negative with a regular lupus anticoagulant test. Then, a contrast enhances computed tomography (CECT) of the chest, abdomen, and pelvis, revealed bilateral axillary, level IV cervical, intercostal, iliac, and inguinal lymphadenopathy. The patient underwent an axillary lymph node biopsy, which showed preserved architecture and with the appearance consisted of reactive lymph nodes. Upper and lower gastrointestinal endoscopies were also done to exclude any evidence of malignancy or any other pathology that can cause blood loss, and where both investigations turned out to be expected. The patient was referred for a haematology opinion, where a bone marrow biopsy was suggested to exclude any haematological malignancy. However, the bone marrow biopsy showed hypercellular bone marrow with normal granulopoiesis, megakaryopoiesis, and absent erythropoiesis, where the possibility of lymphoma was excluded. The patient was treated with corticosteroid and hematinics, where she showed a satisfactory response to improve the cytopenias. The upper limb swelling was also resolved after successful treatment with the anticoagulants. Since the patient's primary concern was the symptoms due to venous thrombosis and cytopenias, the assessment of her joint symptoms was not carried out. Then she was discharged from the hospital with a follow-up plan in two weeks; however, she defaulted to the follow-up.

The subsequent admission was in June 2018 where she was found to have a vasculitic type rash in the lower limb. A skin biopsy showed perivascular inflammatory infiltration predominantly by neutrophils and lymphocytes with focal areas of fibrinoid necrosis suggestive of leukocytoclastic vasculitis. The patient was under investigation for secondary causes for PRCA during this presentation, where the human immune deficiency virus (HIV) screening, viral hepatitis screening (Hepatitis B S antigen and Hepatitis C antibody), parvovirus b19 serology revealed negative results. However, she full filled the American College of Rheumatology (ACR) criteria for rheumatoid arthritis (2) with positive rheumatoid factor level (347 IU/mL) and negative antinuclear antibody (ANA), and anti-double-stranded DNA (dsDNA) levels. The anti-cyclic citrullinated peptide antibody (anti-CCP) level was not done as the patient was not affordable. Overall this patient had transfusion-dependent anaemia for sixteen months, which warranted transfusion of 36 units of the red cell concentrate (RCC).

A multidisciplinary team meeting was held with the participation of a consultant haematologist, and the diagnosis of PRCA secondary to rheumatoid arthritis was made. After that, she was started with oral cyclosporine A 250 mg daily (5mg/kg/day), hydroxychloroquine 200 mg twice daily, and oral prednisolone 40 mg daily, which tailed off over one month. Then she was followed up at the medical and haematology clinic, where she improved and increased the haemoglobin levels without any requirement for further blood transfusions. Her joint pains resolved, and her general wellbeing was markedly

improved. The regular monitoring with full blood counts revealed normal white cell counts and haemoglobin levels in 2 months.

Discussion

Rheumatoid arthritis (RA) is an immune-mediated, chronic, symmetrical, inflammatory disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. These patients often develop destruction in the bones and cartilage of joints, and eventually, the tendons and ligaments weaken [1, 2]. RA should be considered in any patient with joint stiffness, pain, or swelling that persists for more than a few weeks. Joint pain in RA is typically symmetrical, involving multiple joints; however, it may involve 2 to 4 joints asymmetrically or involve a single joint at the onset [6]. RA presents with various extra-articular manifestations evolving over a few weeks to months along with joint symptoms characterized by widespread, persistent synovitis and positivity of autoantibodies to the Fc portion of immunoglobulin G; rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) [2]. Overexpression of tumour necrosis factors (TNF) is a crucial inflammatory element in RA, causing joint inflammation and deformity [2].

According to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis, the diagnosis of RA can be made in patients who have at least one joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease. The classification criteria for RA are based on a scoring system considering four entities. The first one is the joint involvement where involvement of 1 large joint scores 0, 2 to 10 large joints – 1, 1 to 3 small joints (with or without the involvement of large joints) – 2, 4 to 10 small joints (with or without the involvement of large joints) – 3 and > 10 joints (at least one small joint) scoring 5. The second one is the serology where negative RF and negative ACPA scores 0, low-positive RF or low-positive ACPA scores 2, high-positive RF or high-positive ACPA scoring 3. The third entity is the acute-phase reactants where normal CRP and normal ESR scoring 0 and abnormal CRP or abnormal ESR scoring 1. The final entity is the duration of symptoms where < 6 weeks scores 0 and ≥ 6 weeks scores 1 [7]. Our patient fulfilled the 2010 ACR/EULAR criteria for RA, where the diagnosis was made. Presentation of the RA can be very heterogeneous in some patients associated with other autoimmune diseases. PRCA associated with RA is reported in the literature though it is not common [8, 9].

PRCA is a hemopoietic disorder first reported in 1922. The whole mark of the disease is normocytic normochromic anaemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow [3]. It can be primary (congenital) or acquired secondary to viral infections, autoimmune diseases, drugs, and toxins [5]. Other secondary causes of acquired PRCA include lymphoproliferative disorders, pregnancy, hematologic malignancies, nonhematologic neoplasms, of which the association with thymoma is the best known [5]. There are numerous cases of PRCA that have been reported as a secondary manifestation of RA [10–18]. Among them, four cases had eosinophilic fasciitis along with PRCA [12]. Some cases have been reported with PRCA associated with both RA and parvovirus B19 infection, and there were several cases of PRCA associated with pregnancy and systemic-

onset juvenile idiopathic arthritis [13, 15, 16]. One case has been reported of PRCA secondary to D penicillamine treatment in RA [18].

Pathogenesis of PRCA is heterogenous where it involves immune dysfunction with antibodies directed against erythroid precursor cells or erythropoietin or due to T cell-mediated suppression of erythropoiesis [10, 19]. The immunoglobulin (IgG) mediated inhibition of haemoglobin synthesis or complement-binding and direct cytotoxic effect on erythroblasts were found in patients with PRCA, wherein in some patients, the inhibitory antibodies were directed against erythropoietin [20]. Various autoimmune mechanisms of PRCA have been described, such as antibodies against erythroblasts or erythropoietin. T cells or natural killer (NK) cells have been proposed to secrete factors selectively inhibiting erythroid colonies in the bone marrow or directly lysing erythroblasts. Lysis of erythroblasts by T cells could result from 'classic' T-cell receptor (TCR)- mediated antigen recognition. In addition, PRCA can be mediated by major histocompatibility complex (MHC) unrestricted effector-target cell recognition, as erythroid progenitors progressively lose expression of MHC class I and, thus, become susceptible to destruction by NK-type cells. This mechanism is similar to NK-mediated lysis of tumour cells following the loss of HLA class I by the tumour cells [19]. The final result of all these mechanisms is anaemia with bone marrow examination revealing a complete absence of erythroblasts but normal granulocytic and megakaryocytic series [21].

The patients with PRCA present with symptoms of severe anaemia in the absence of haemorrhagic phenomena [19]. Because there is pure underproduction anaemia in PRCA, the gradual decline in haemoglobin concentration allows some degree of adaptation, and symptoms may be less than expected for the degree of anaemia [5]. Of course, patients with secondary PRCA may manifest the symptomatology of the associated syndrome [5]. The findings of the haematological investigations will be normochromic normocytic anaemia with low reticulocyte count (less than 1%) with normal platelet count, leucocyte count, and leucocyte differentials [5, 19]. In the setting of concurrent inflammation, there may be some modest reduction in the total white blood count or a mild abnormality (either slightly high or slightly low) in the platelet count. There may also be a mild relative lymphocytosis [5]. The bone marrow examination will reveal a complete absence of erythroblasts with normal granulopoiesis and megakaryopoiesis [10, 18, 19]. As with all diagnostic examinations of the bone marrow for cytopenias, the materials should be collected for cellular immunology, cytogenetics, and clonal analysis of T-cell receptors. Abnormal cytogenetics in the setting of a characteristic marrow for PRCA indicates the myelodysplastic variant of PRCA. If increased lymphocytes or plasma cells are present, they should be polyclonal in acquired immune PRCA. If clonal lymphocytes are present, it suggests PRCA secondary to an associated lymphoproliferative disorder. T-cell-receptor gene rearrangement studies should be performed routinely [22]. In all patients with marrows diagnostic of PRCA, B19 parvovirus testing should be performed, and in adults with PRCA with evidence of parvovirus infection or of a disorder associated with secondary PRCA, a computed tomography scan of the chest should be performed to rule out a thymoma, which would have potential therapeutic implications [19]. Our patient had anaemia with low reticulocyte count, normal platelets counts and the leucopenia was considered immunological in origin. We confirmed PRCA in our patient by the bone marrows biopsy, where there was a marked reduction in erythroid lineage with normal megakaryopoiesis and increased granulopoiesis. A viral screen for a

possible aetiology, autoimmune screen, and CECT to exclude thymoma was done to rule out other secondary causes for PRCA other than RA in this patient.

Depending on the cause, the course of PRCA can be acute and self-limiting or chronic with rare spontaneous remissions [19]. Otherwise, treating PRCA varies with the aetiological factors; however, for primary acquired autoimmune PRCA or secondary PRCA refractory to other therapy, the treatment of choice is immunosuppression [5, 17]. The therapeutic plan usually focuses on the sequential use of various immunosuppressive therapies, including corticosteroids, cyclophosphamide, cyclosporin A and anti-thymocyte globulin, splenectomy and plasmapheresis until remission is obtained [10]. Corticosteroids have been considered the treatment of the first choice, although relapse is not uncommon. Cyclosporin A has become established as one of the leading drugs for the treatment of PRCA. Recently, the efficacies of the anti-CD20 monoclonal antibody, rituximab and anti-CD52 monoclonal antibody, alemtuzumab, to induce remissions of therapy-resistant PRCA have also been reported [10].

In principle, PRCA secondary to autoimmune/collagen vascular disorders may respond to therapy specific to the management of those disorders. In practice, the treatment of these disorders is usually immunosuppression, and in cases where alternative disease-modulating therapy is available, the patient is usually referred to the haematologist because it was ineffective [5]. The goal of treatment is to induce remission to attain an average haemoglobin concentration with the recovery of erythropoiesis without any requirement for transfusion and avoiding problems associated with transfusions; a partial response is the attainment of transfusion independence with a low but clinically acceptable haemoglobin concentration [4, 5]. Our patient has been treated with prednisolone 40 mg daily, which tailed off over one month with concurrent treatment of cyclosporin A and hydroxychloroquine, where she attained complete recovery within two months.

The clinical outcome of PRCA is variable from complete remission to fatal, and it depends upon the cause and the types of treatment [11, 18, 23]. Some patients with PRCA show no response to treatment [11]. In pregnancy-associated PRCA, cyclosporine and other immunosuppressive agents may significantly affect the fetal outcome and maternal morbidity and probably should be avoided [5]. Naparuck et al. has reported favourable treatment response in groups of parvovirus B19 infection, drug- (non-erythropoiesis-stimulating agent (ESA)-) induced PRCA and idiopathic PRCA. The outcome has been unfavourable in groups of ESA and thymoma-induced PRCA, even they were receiving immunosuppressants or chemotherapy, respectively [23]. However, Hirokawa et al. has reported cyclosporine producing excellent responses in patients with thymoma-associated PRCA, although limited information suggests that patients with thymoma-associated PRCA have poor prognoses [24]. At the same time, continuous immunosuppression is associated with an increased risk of infection and malignancy; therefore, adequate prevention of infection will be essential [24]. Nevertheless, our patient did not develop any complications due to immunosuppressive therapy.

The final diagnosis of our patient was long-standing deforming rheumatoid arthritis complicated with PRCA with immune-mediated leukopenia and vasculitis. The challenges in the diagnosis were to exclude the possible other aetiologies of the PRCA, leukopenia, generalized lymphadenopathy and venous thrombosis in an unusual site. Extensive lymphadenopathy and venous thrombosis were also reported in patients with rheumatoid arthritis [25]. A nationwide cohort study done in Taiwan recruiting nearly 30000 RA patients has shown a 3.36 fold increased risk of deep venous thrombosis and a 2.07 fold increase in pulmonary embolism than patients without RA [26]. A study done in the United Kingdom has also concluded a similar result [27]. Lymphadenopathy is also a clinical manifestation of RA, indicating the disease activity [28]. Some studies found that the overall frequency of lymphadenopathy in patients with RA is as high as 82% and mainly involving axillary lymph nodes [29]. Lymphadenopathy at unusual sites has also been reported in patients with RA, contributing to venous thrombosis at unusual sites due to vascular compression [30]. Venous thrombosis involving the axillary vein in our patients may be attributed to the fact of possible lymphadenopathy. We excluded the possibility of haematological malignancy by doing a lymph node biopsy and repeating bone marrow biopsy as both of them showed no evidence of leukaemia or lymphoma. The thrombophilia screen also excluded the antiphospholipid syndrome, and the overlapping SLE was also excluded due to not satisfying the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [31]. Hence these manifestations were thought to be an immune-mediated phenomenon due to rheumatoid arthritis at the multidisciplinary team involving a haematologist.

The major drawback to start immunosuppressive drugs was leukopenia. Nevertheless, after starting cyclosporin A, hydroxychloroquine and steroids, she showed a marked improvement [32]. Cyclosporin A has proven to be the drug of choice for PRCA, and the second-line therapy for PRCA include anti-thymocyte globulin (ATG) and cyclophosphamide [3, 33, 34]. She was transfusion dependent for nearly 16 months, but she was completely free of blood transfusion after the treatment. Her joint deformities were fixed but minimally interfering with daily living activities, and her constitutional symptoms were also improved.

Patient Perspective

The patient had mild joint symptoms, although with joint deformities where she did not complain about them until the direct questioning. Her main concern was the acute symptoms she got due to the cytopenias in the first two episodes and venous thrombosis in the second episode. However, the patient was educated about the disease after the third episode, where she was satisfied with the treatments she received after the complete diagnosis of PRCA secondary to RA.

Conclusion

PRCA is a disabling illness that may lead to transfusion-dependent anaemia, causing transfusion-related complications. RA is a known cause for secondary acquired PRCA due to the disease itself or the RA treatments. The patients with PRCA present with symptoms of severe anaemia, which may be less

pronounced due to adaptation with gradual haemoglobin drop. Blood analyses and bone marrow examination can diagnose PRCA, and investigating for a secondary cause is of the essence due to its therapeutic importance. Sometimes the diagnosis of PRCA secondary to RA can be challenging due to the presence of leukopenia, lymphadenopathy and venous thrombosis at unusual sites due to immunologic and vasculitic phenomena. The treatment of choice for PRCA is immunosuppression which includes multiple modalities, and the goal of treatment is to recover erythropoiesis without any requirement for transfusion and avoid problems associated with transfusions. The clinical outcome of PRCA can be variable through early diagnosis, and commencing treatments are crucial for a better prognosis and to prevent irreversible complications, and most evidence-based treatment will significantly improve the outcome.

Abbreviations

RA: Rheumatoid arthritis; PRCA: Pure red cell aplasia; ACR: American College of Rheumatology; CECT: contrast-enhanced computed tomography; Hb: Haemoglobin; MCV: Mean corpuscular volume; MCHC: Mean corpuscular haemoglobin concentration; NSAID: Non-steroidal anti-inflammatory drugs; HIV: human immune deficiency virus; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; ANA: Antinuclear antibody; Anti dsDNA: Anti double-stranded deoxyribonucleic acid; TNF: tumour necrosis factors; ATG: anti-thymocyte globulin

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors were involved in the management of the patient and generating the concept. All authors made an intellectual contribution and wrote the paper. All authors read and approved the final manuscript.

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Figures

Figure 1

Boutonniere deformities in the left middle, right middle and right ring fingers shown as a side view (A) and a front view (B)

Supplementary Files

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