CASE REPORT AND BRIEF REVIEW OF LITERATURE
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Pure Red Cell Aplasia as a Presenting Feature in Systemic Lupus Erythematosus and Association with Thymoma, Hypothyroidism and Hypoparathyroidism: a Case Report and Literature Review

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ABSTRACT

This paper presents a 54-year-old female with lupus whom severe anaemia due to pure red cell aplasia (PRCA) was the first manifestation. There was seven years interval between PRCA onset and diagnosis of lupus. Thymectomy due to thymoma had been carried out six years before but anaemia sustained.

Hypothyroidism and hypoparathyroidism were other associated diseases. Severe anaemia and the need for monthly blood infusions were resolved following treatment with Prednisolone, Hydroxychloroquine and Levothyroxine.

Keywords: Hypothyroidism; Hypoparathyroidism; Red-Cell Aplasia; Systemic lupus erythematosus; Thymoma

INTRODUCTION

Pure red cell aplasia (PRCA) or erythroblastopenia refers to a rare type of anaemia affecting precursors of only red blood cells. In PRCA, the bone marrow ceases to produce red blood cells. This condition was first described by Paul Kanzelson in 1922. The pathophysiology of PRCA is not completely understood but may be related to abnormal T-cell function and the presence of IgG antibodies which target precursors of erythrocytes and erythropoietin. The Characteristics of PRCA include severe anaemia, reticulocyte count of less than 1% and mature erythroblasts of less than 0.5% in the bone marrow whereas immature erythrocyte progenitors are present in bone marrow (maturation arrest). White blood cell and platelet maturation are normal. The bone marrow is usually normocellular.[1] Acquired PRCA may occur for unknown reasons (idiopathic) or as a primary autoimmune disease or as an associated disorder with other autoimmune diseases (lupus, type 1 diabetes mellitus, thyroiditis, rheumatoid arthritis and Sjögren syndrome). There are also several reports of PRCA secondary to thymoma, viruses (parvovirus B19, HIV, herpes or hepatitis), hematologic malignancies (hair

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cell leukemia, B and T-cell chronic lymphocytic leukemia, large granular lymphocytic leukemia and lymphoma), autoimmune haemolytic anaemia, certain drugs (recombinant human erythropoietin, Rifampicin, Diphenylhydantoin, Carbamazepine, Lamivudine, Cyclosporin, Rituximab, Mycophenolic acid), pregnancy, renal failure and good syndrome (thymoma with combined T-cell and B-cell deficiency).[2-11]

In this report, we describe a case with pure red cell aplasia associated with thymoma. Systemic lupus erythematosus (SLE) and also, hypothyroidism and hypoparathyroidism diagnosed several years later after thymectomy. A review of literature is also, included.

CASE REPORT

The patient gave informed consent before participating in the study and the study protocol was in accordance with the ethical standards of 1964 declaration of Helsinki.

A 54-year old female was admitted to the rheumatology division due to arthritis and anaemia, in the early spring of 2012. Her main problem (severe normocytic anaemia with haemoglobin 3.4 and reticulocyte 0.5%) was started seven years ago. Clinicopathologic evaluation by haematologist illustrated pure red cell aplasia (Figures 1 and 2) and also, thymoma (without any symptoms such as dyspnoea) in chest CT scan which established after thymectomy and pathologic assessment, 6 years prior to the study (Figures 3 and 4).

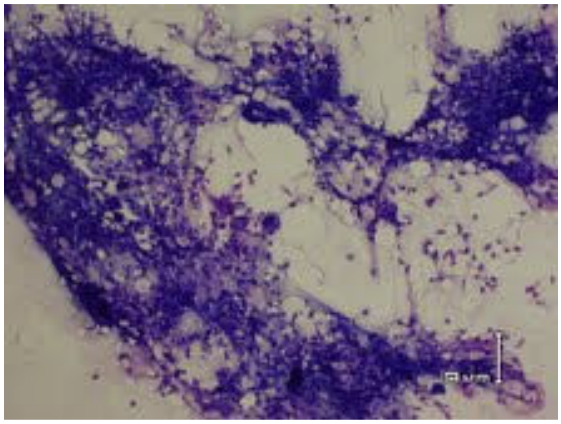

Figure 1. Hypo-cellular bone marrow with decreased erythroid series, Giemsa staining (light micrograph ×40)

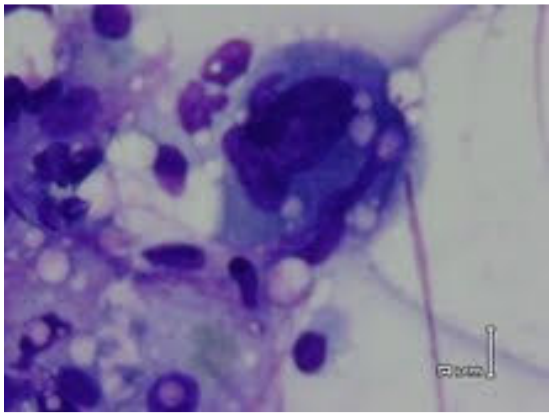

Figure 2. Presence of megakaryocyte and a few myeloid series without obvious islands of erythroid series in bone marrow, Giemsa staining (light micrograph ×1000)

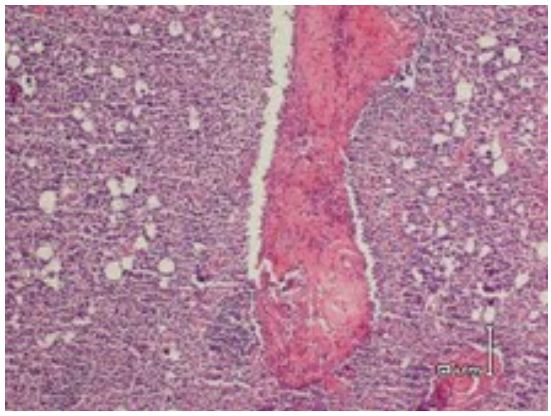

Figure 3. Lobulated thymoma with heavy infiltrations by lymphocytes admixing with epithelial nests and involutionary fatty stroma, H & E staining (light micrograph ×40)

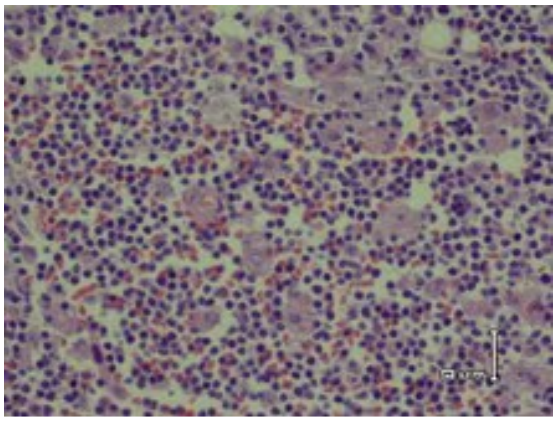

Figure 4. Lymphocytic thymoma with predominant T-lymphocytes and floating of islet of epithelial nests, H & E staining (light micrograph ×400)

At that time, laboratory and pathologic assessment including anti-nuclear antibody (ANA), anti-double stranded DNA, bone marrow aspiration and biopsy and flow-cytometry (to rule out hematologic malignancy) were all unremarkable. Anaemia sustained despite surgical removal of thymus gland. At the time of current admission, it has been seven years since she began to receive two units of red blood cells monthly.

On current admission, physical examination by rheumatologist revealed pallor, bronze colored skin and generalized puffiness. Swelling and tenderness were observed in second metacarpophalangeal and proximal interphalangeal joints of right hand and wrist joint of left hand. There was no xerostomia, xerophthalmia or clues compatible with myasthenia. Evaluation of the patient revealed anaemia [haemoglobin: 8.7 mg/dL, mean cell volume (MCV): 85 fL], reticulocyte count 0.8%, serum iron (Fe) level: 109 µg/dL, total iron binding capacity (TIBC): 196 µg/dL, LDH: 924 U/L (normal<480), normal Serum B12 and folate level, negative anti tissue transglutaminase antibody (anti TTG) and normal haemoglobin electrophoresis. Other paraclinical characteristics were recorded as follows: erythrocyte sedimentation rate (ESR)=116, C-reactive protein=1+, lymphopenia without Leukopenia or thrombocytopenia (WBC: 7400/µL, lymphocyte: 19%, PMN: 68%, platelet: 237000/µL), proteinuria (up to 900 mg/24 hours in collected urine sample), bland urine sediment, hypocalcaemia (Ca: 5.9 mg/dL), hyperphosphatemia (P: 7.2 mg/dL), (ANA)=1/320 (normal<1/10, pattern: homogenous), anti-double stranded DNA=66 U/mL (normal <25) and right sided pleural effusion in chest CT-scan. Positive ANA and anti-DNA were confirmed by re-checking in another laboratory. Diagnosis of SLE was confirmed based on 1997 update of the 1982 revised American College of Rheumatology (ACR) classification criteria for lupus.[12] High LDH of serum might be due to associated haemolytic anaemia. Immunoglobulin electrophoresis revealed no immunoglobulin deficiency. Evaluation of serum for Hepatitis B, C and HIV (HBs Ag, HCV Ab and HIV Ab) were reported negative. Serum antibodies for parvovirus B19 was reported negative for IgM and positive for IgG by an ELISA method. No lymphadenopathy or organomegaly was found in chest CT or abdominopelvic ultrasound.

Hemosiderosis (secondary to blood infusions) was strongly suggested regarding generalized bronze colored skin, transferrin saturation>50%, ferritin>1200 ng/ml and abnormal liver enzymes [SGOT=93 u/l (normal<31), SGPT=44 u/l (normal<31)]. An extended clinical investigation was performed to disclose associated disease and co-morbidities with pure red cell aplasia. Rheumatoid factor (RF) and anti-citrullinated protein antibody (anti-CCP) were reported negative. Thyroid function test suggested hypothyroidism as an associated disease which was confirmed by re-checking of TSH [T4=5 nmol/dL (normal: 6-12), TSH=12 µIU/mL and 22.7 µIU/mL (normal: 0.25-5), T3RU=26% (normal: 25-35%)]. Evaluation of hypocalcaemia showed hypoparathyroidism as an associated endocrine disease [Ca=5.9 mg/dL, P=7.2 mg/dL, alkaline phosphatase=500 U/L, PTH=14.9 pg/mL (normal: 15-65)]. Rapid ACTH test did not show adrenal insufficiency.

Hydroxychloroquine (400 mg/day) and Prednisolone (40 mg/day=1 mg/kg) were started. Prednisolone was tapered after one month. Levothyroxin (100 micrograms/day), Calcitriol (0.25 micrograms/day) and Calcium carbonate (1000 mg/day) were started for hypothyroidism and hypocalcaemia, respectively (after endocrinology consultation). The patient was also treated by Deferoxamine (1000mg) three times a week as an iron chelator drug (after haematology consultation). She also, received Alendronate (70 mg/weekly) for the osteoporosis which was documented by bone mass densitometry with dual energy X-ray absorptiometry scan (T score for femoral neck: -3.6 and for lumbar spine: -1.87). Two months later, pleural effusion and proteinuria were resolved. Haemoglobin level increased to 12 mg/dl and there was no need to red blood cell infusion. Therefore, Prednisolone was tapered gradually. Six months later, Haemoglobin, calcium, phosphate and TSH were reported in normal range levels which resulted in tapering of Prednisolone to 10 mg/day. Ferritin level and transferrin saturation decreased to less than 500 ng/ml and less than 50%, respectively. Deferoxamine was discontinued by haematologist.

DISCUSSION

Association of pure red cell aplasia with lupus is rare. To date, there have been around 20 reported cases with these two disorders. SLE was diagnosed concurrently or prior to diagnosis of PRCA in majority of these cases. In minority of cases in which SLE

diagnosis followed the diagnosis of PRCA, the interval between them was not reported longer than 4 years.[9, 11, 13-15] That was contrary to the disease course of presented case in which lupus was diagnosed about 7 years after PRCA. Clinical manifestations of patients with SLE and PRCA were not different from lupus patients in general except for less frequent pleuritis and a trend for less proteinuria and hallucination in the former group.[9]

There are also, rare case reports of SLE associated with PRCA and autoimmune haemolytic anaemia.[16]

To the best of our knowledge, there are four previous reports of cases with lupus, PRCA and thymoma, collectively in the same patient.[17-20] One of them developed PRCA 3 years after thymectomy and another one was a case with lupus- like disease who developed PRCA and thymoma 9 years later. All patients were female with age ranges from 49-76 years. They had quiescent SLE at the time of PRCA diagnosis and were treated with blood transfusion and Prednisolone. One of them received biologic therapy (Rituximab) as well. Two patients died from pneumonia within two months after PRCA was diagnosed. One patient died due to pulmonary emboli one year after diagnosis of PRCA and the fourth patient died within several weeks after diagnosis of PRCA and thymectomy (due to anaemia and pulmonary emboli).

Lupus in association with PRCA and hypothyroidism has been reported rarely. To our knowledge, four case reports with these disorders together were found in literature.[21-24] There are also, several reports for association of other autoimmune diseases with thymoma including: lupus, PRCA and myasthenia gravis. SLE can be associated with thymoma, particularly in older patients. Prevalence of SLE in patients with thymoma has been estimated in clinical studies as 1.5-2%.[25] SLE was diagnosed before, concurrently or after diagnosis of thymoma in these reports and clinical picture of lupus was as classical form.[25-30]

In the current case study, a patient with SLE was reported in which PRCA was her presenting feature. PRCA is a rare clinical manifestation and an unusual cause of anaemia in SLE. Several reports for association of PRCA with lupus were seen in the literature.[9] However, occurring PRCA, lupus and thymoma together or association of PRCA with lupus and hypothyroidism collectively in the same patient have rarely been reported.[17-24]

To the best of our knowledge, this is the first report of the occurrence of PRCA, thymoma, lupus, hypothyroidism and hypoparathyroidism collectively in one patient. There was seven years interval between emergence of pure red cell aplasia and diagnosis of SLE in this case. Hypothyroidism and hypoparathyroidism might be as a result of associated autoimmune diseases. However, secondary hemosiderosis might be another cause for hypothyroidism and hypoparathyroidism.

Therapeutic strategy and prognosis of secondary PRCA is directly related to the management and the course of underlying disorder, respectively. Underlying conditions such as thymoma or autoimmune diseases should be treated. Thymectomy or gamma irradiation of the thymus gland should be performed for thymoma. As mentioned before, up to 30% of PRCA cases due to thymoma are reversed by thymectomy. In the reported case, anaemia did not improve after thymectomy and even, clinical and immunologic features of SLE were emerged as an associated responsible autoimmune disease several years later. Worsening the disease course or developing clinical features of SLE and PRCA following thymectomy has been reported in other cases, as well.[20, 25, 31] Usually, majority of PRCA cases with lupus respond to corticosteroids within 4-6 weeks. However, complete tapering is unlikely in many patients. In corticosteroid dependent patients or refractory cases, immunosuppressive drugs including Cyclosporine, Cyclophosphamide, intravenous immunoglobulins and also, Erythropoietin and plasmaphresis have been used.[2, 32] Danazol is also an option for refractory cases.[14] Spontaneous remission may also occur in 5-10% of cases with PRCA.[2]

Secondary PRCA which has not responded to therapeutic management of the underlying disease is also treated as an immunologically mediated disease. Rituximab, Alemtuzmab, anti-thymic globulin (ATG), autologous and nonmyeloablative allogenic peripheral stem cell transplantation have also been used in refractory cases with variable results.[2, 32] In refractory PRCA cases that have been complicated by hypersplenism, splenectomy might be indicated. Even though, it has not been effective in majority of cases.[33]

Prognosis of PRCA is not only influenced by natural course of underlying disease but also by therapeutic complications. Hemosiderosis can develop in multi-transfused patients. Corticosteroid therapy can lead to osteoporosis and infections. These

complications had been occurred in the presented case and were managed by discontinuing blood transfusion, iron chelating therapy with Deferoxamine and with calcium, vitamin D supplement and bisphosphonate. PRCA may also, evolve into aplastic anaemia and acute myelogenous leukemia. Infections acquired during blood transfusions can also affect prognosis.

Taking into consideration the lupus as a responsible cause of PRCA, Prednisolone and Hydroxychloroquine were started for the presented patient. Anaemia as well as arthritis, pleural effusion and proteinuria were resolved. Anaemia did not relapse after tapering Prednisolone to 10 mg/day. Treatment of hypothyroidism with Levothyroxin might have been a role as an adjunct therapy to treat PRCA in this case; as thyroid hormones have been assumed to increase the effect of erythropoietin in the formation of erythroid clones in vitro.[34]

The disease course in this patient showed that PRCA as a haematological feature of SLE may appear rarely a long time before other manifestations. SLE should be considered in differential diagnoses for any case with PRCA, even with negative early report for ANA and anti-DNA. This necessitates rheumatology consultation, regular monitoring for other symptoms and signs of lupus as well as re-checking serologic tests (ANA and anti-DNA) during the follow-up. Also, bearing in mind that PRCA may be a clue to the association with other systemic diseases, clinical search for associated disorders (thymoma, lymphoproliferative disorders, etc.) appears helpful.

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