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CASE REPORT

Acquired amegakaryocytic thrombocytopenia and red cell aplasia in a patient with thymoma progressing to aplastic anemia successfully treated with allogenic stem cell transplantation

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Abstract
Association of pure red-cell aplasia with thymoma is well documented. However, acquired amegakaryocytic thrombocytopenia (AAMT) has been rarely associated with thymoma with only five reported cases in literature. We report a patient with thymoma complicated by pure red cell aplasia (PRCA) and AAMT who progressed to develop aplastic anemia (AA). The patient was refractory to 10-months of immunosuppressive therapy with cyclosporine, prednisone, and antithymocyte globulin. She was eventually treated with allogeneic stem cell transplantation (allo-SCT). On Day +323 the patient continues to be transfusion-independent. This case illustrates how in patients with thymoma and AAMT may herald development of AA. This is also the first report of a patient with AAMT progressing to thymoma-associated AA being successfully

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treated with allo-SCT. The successful outcome suggests allo-SCT as a feasible option similar to other AA patients.

Introduction

Association of pure red cell aplasia (PRCA) with thymoma has been well documented [1—3]. However, acquired amegakaryocytic thrombocytopenia (AAMT) has been rarely associated with thymoma. The treatment of both conditions with immunosuppressive therapy (IST) has shown encouraging results; however, patients can still progress to aplastic anemia (AA). We report a patient with thymoma complicated by red cell aplasia (RCA) and AAMT with progression to AA who was successfully treated with allogeneic stem cell transplantation (allo-SCT).

Case report

A 61-year-old woman with history of thymoma was referred to us for pancytopenia with severe thrombocytopenia. She had been diagnosed with lymphocyte-rich thymoma for which she received four cycles of neoadjuvant CAPP chemotherapy (cisplatin, doxorubicin, cyclophosphamide, and prednisone). She subsequently underwent radical thymectomy 8 weeks prior to presentation. At presentation, she had progressive fatigue, dyspnea on exertion, and petechial rash. Her hemoglobin was 7.7 g/dL, platelet count $2 \times 10^3/\mu L$, white blood cell (WBC) count $3.2 \times 10^3/\mu L$, reticulocyte count 0.4%, and absolute neutrophil count (ANC) $1460/\mu L$. Blood smear showed anisopoikilocytosis, ovalocytes, and markedly decreased platelets but was otherwise unremarkable. No evidence of thymoma recurrence or residual disease was seen on computerized tomography. Bone marrow biopsy showed normocellular marrow (40% cellularity) with myeloid:erythroid ratio of 24.7:1, erythroid and megakaryocytic aplasia with left-shifted myeloid maturation, without any increased blasts or evidence of myelodysplastic syndrome. Hence a diagnosis of amegakaryocytic thrombocytopenia (AAMT) and pure red cell aplasia (PRCA) was made.

The patient was started on cyclosporine 4 mg/kg daily, eltrombopag 50 mg daily (later increased to 150 mg daily), and prednisone 60 mg daily tapered over 4 weeks. As her blood counts did not improve, a repeat bone marrow 1 month later showed hypocellular marrow (<5% cellularity) with residual lymphocytes and plasma cells. Trilineage hematopoiesis was absent, indicating progression to aplastic anemia (AA) (Fig. 1). The patient received horse antithymocyte globulin (ATG) 40 mg/kg/d and methylprednisolone 1 mg/kg/d on Days 1—4 followed by prednisone 1 mg/kg/d on Days 5—9. She continued to receive the same doses of cyclosporine and eltrombopag. Her bone marrow recovered transiently 3 months after ATG, showing variable cellularity up to 30% and reemergence of megakaryocytes with some dysmegakaryopoiesis and clustering. However, despite 10 months of IST, she remained severely pancytopenic and transfusion-dependent for both red cells and platelets.

Due to failure of sustained hematopoietic recovery, the patient underwent matched unrelated donor stem cell transplantation (SCT) 10 months after her initial diagnosis of AAMT and PRCA. The preparative regimen consisted of daily intravenous fludarabine ($30\ mg/m^2$) and cyclophosphamide ($300\ mg/m^2$) on Days −6 to −2 with addition of intravenous alemtuzumab (20 mg) on Days −5 to −3. Neutrophil engraftment and platelet engraftment were achieved on Day +11 and Day +21, respectively. She was discharged only on tacrolimus for graft-versus-host disease prophylaxis. One-month posttransplant, she developed cytomegalovirus reactivation, which was treated with ganciclovir.

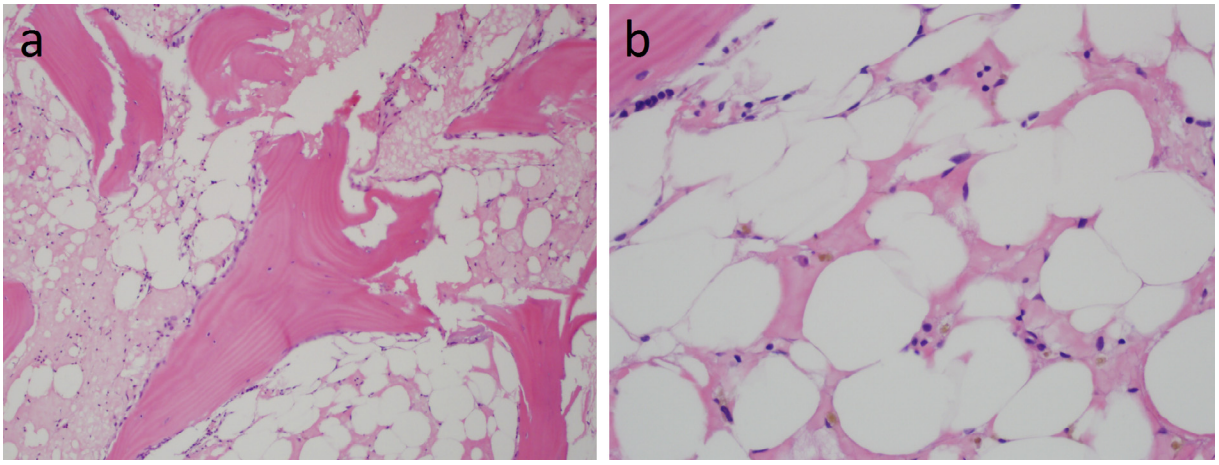

Fig. 1 Bone marrow biopsy, haemotoxylin and eosin stain. (A) 100×; (B) 400×x showing hypocellular marrow (cellularity: <5%) with residual lymphocytes and plasma cells, and no normal trilineage hematopoiesis. *Note*. H&E = haemotoxylin and eosin.

The patient has not required any platelet transfusions since Day +14 and tacrolimus was discontinued 7 months after transplantation. Bone marrow examination on Day +35 showed 40% cellular marrow with trilineage hematopoiesis. Bone marrow chimerism studies on Day +61 showed 100% myeloid donor cells, but 0% donor T-cells. The patient was monitored for another 4 months without interventions. Repeat bone marrow biopsy 6 months after SCT showed 60% cellularity with trilineage hematopoiesis and relative erythroid hyperplasia. Chimerism study at the same time showed identical microsatellite polymorphism pattern to the donor compatible with successful engraftment and 100% myeloid donor cells, T-cell microsatellite polymorphism analysis was suboptimal. On Day +323, the patient had sustained counts of platelets in the range of 36—45 $\times$ $10^3/\mu L$, hemoglobin in the range of 7—9 g/dL, WBC in the range of 1.0—1.7 $\times$ $10^3/\mu L$, and ANC in the range of 0.85—1.2 $\times$ $10^3/\mu L$. A repeat chimerism study at the same time revealed 100% of myeloid cells and 46% of T-cells of donor origin. The patient remains transfusion-independent of both red cells and platelets. Chest imaging has not shown any recurrent thymoma.

Discussion

Thymoma is the most common tumor of the anterior mediastinum with an incidence of ~0.13 per 100,000 person-years in the United States [1,2]. There is a strong association between thymoma and paraneoplastic immunological disorders, sometimes with hematological manifestations in the form of PRCA or rarely, AA or AAMT [2—10].

PRCA is the most common hematologic paraneoplastic manifestation of thymoma and is present in nearly 5% of cases [7]. A total of 25—30% of patients with PRCA achieve complete remission (CR) after surgical resection of thymoma alone [7]. A recent review comparing different IST regimens showed CR in 38% (5/13) of patients with corticosteroids after thymectomy, 80% (16/20) in patients with cyclosporine after thymectomy, and 100% in patients with cyclophosphamide-based regimen (1/1) [8]. Rituximab and alemtuzumab have also shown some efficacy in relapsed or refractory cases, however >60% of the reported patients continued to be transfusion-dependent [7—10].

Thymoma has been rarely associated with AAMT with only five reported cases in the literature [11—14]. It is important to differentiate this entity from megakaryocytic hypoplasia which has been reported after thymectomy [12]. In AAMT there is marked thrombocytopenia with selective absence of megakaryocytes and normal myeloid precursors, with normal or decreased marrow cellularity [11]. Out of the five cases reported to date, four were also associated with PRCA [12—14]. All patients were initially diagnosed with PRCA and subsequently progressed to AAMT [11—14]. Remarkably two of the cases, including ours, continued to progress to AA despite immunosuppression. There have been cases of AAMT not associated with thymoma that have also shown rapid progression to AA [15]. The rapid progression of PRCA and AAMT to AA in these cases suggests that thymoma-associated AAMT may have a more aggressive disease course than patients with thymoma-associated PRCA.

There is only one successfully treated case of thymoma-associated PRCA and AAMT in the literature [14]. This patient, who had thymectomy 10 years prior, had failed frontline corticosteroids and cyclosporine (400 mg/d) but achieved CR with the addition of ATG (40 mg/kg/d) [14]. Notably, there is another reported case of PRCA and AAMT but without thymoma who achieved CR with second line ATG after failing cyclosporine and corticosteroids [16]. AAMT not associated with thymoma has been treated successfully with allogeneic SCT as well [17].

Thymoma-associated AA is relatively rare [10,18]. The largest literature review evaluated 24 manuscripts published between 1958 and 2013 with 27 patients showing aplastic or hypocellular marrow. None of them achieved remission with surgery alone. Nine cases treated before 1972 did not receive cyclosporine or ATG and all patient expired secondary to hemorrhage or septic shock [10]. After 1980, 15 patients received cyclosporine-based therapy, 10/15 responded to the therapy with a response rate of (67%). Eight patients (53%) achieved CR and two patients (13.3%) achieved partial response (PR). Only two patients were treated with allogenic SCT for refractory disease or metastatic thymoma [10]. Interestingly, resection of the thymoma has shown no impact in the clinical course of AA [18]. More recent case reports continue to demonstrate good outcomes with cyclosporine and corticosteroids regimens [18,19]. The gold standard today in elderly patients and those without HLA compatible donors therefore continues to be IST.

As discussed before, there is only anecdotal evidence in the form of two case reports to support SCT for thymoma-associated severe AA [20—22]. Independently of the cause of AA, it is widely accepted that those who fail IST therapy are undoubtedly candidates for SCT with a 10-year survival estimate of 64% [20]. Given the encouraging results in our case, we provide further evidence to support SCT in patients who develop thymoma-associated PRCA and/or AAMT progressing to AA. Based on the prior cases reports of thymoma associated AAMT, including our case, patients with these conditions may warrant consideration for SCT and discussion of possible therapeutic options after IST. Further prospective studies will be required to determine the overall survival and response of patients with AAMT and thymoma who undergo SCT after failing conventional therapy.

Conflicts of interests

The authors have no conflict of interests.

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