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ORIGINAL ARTICLE

Thymoma-associated pancytopenia: immunosuppressive therapy is the cornerstone for durable hematological remission

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Abstract Pancytopenia is a very rare complication of thymoma and has been sporadically reported in only a few cases. We report a case of a 68-year-old woman who presented with pancytopenia associated with thymoma. After failing high-dose corticosteroids, she responded to cyclosporine treatment and underwent successful thymectomy. We also reviewed all other similar cases published in the English language literature. Surgical resection by itself was generally ineffective for treatment of pancytopenia, and immunosuppressive therapy was required for bone marrow recovery. Resolution of pancytopenia was most frequently associated with cyclosporine-based therapy with a response rate (RR) of 66.6 %. In conclusion, pancytopenia associated with thymoma requires medical treatment, and the evidence presented here suggests that a cyclosporine-based regimen should be considered for initial therapy.

Keywords Thymoma · Pancytopenia · Aplastic anemia

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Introduction

Thymic tumors usually originate in the epithelial layers of the gland and are rare. The incidence has been estimated to be 0.15 per 100,000 person years [1]. They are usually slow growing and spread by local extension, where distant spread via metastasis is rare. Surgical resection is the mainstay of treatment. Combination of cytotoxic chemotherapy and radiation therapy is used in metastatic and locally advanced disease, respectively. Thymic tumors can be commonly associated with various autoimmune phenomena, such as myasthenia gravis. Hematologic autoimmune manifestations are rare. Pure red cell aplasia is the most common hematologic phenomena and accounts for about 2–5 % of the thymoma cases [2]. Pancytopenia or aplastic anemia is rarely associated with thymoma but has been sporadically reported in the literature. Surgical resection is the mainstay of treatment for thymoma. It is unknown whether surgical resection alone results in resolution of the pancytopenia or medical management is imperative. Additionally, thrombocytopenia and absolute neutropenia associated with bone marrow failure in these cases make surgical resection a challenge. Here, we present a case of pancytopenia associated with thymoma and comprehensively review all the cases in the English language literature until December 2013 to analyze the demographics and review the efficacy of surgical and medical management in thymoma-associated pancytopenia/aplastic anemia.

Methods

A systematic MEDLINE search was performed for the terms "Pancytopenia and Thymoma" and "Aplastic anemia and Thymoma" up to December 2013. A total of 210 articles were retrieved. Only manuscripts written in the English language, describing aplastic anemia or pancytopenia associated with

thymoma, were considered after review of the title and abstract where available. Cases were included if they had pathologic diagnosis of thymoma and laboratory evidence of pancytopenia and/or if they had pathologic diagnosis of bone marrow aplasia. Cases were excluded if they had pure red cell aplasia, concomitant paroxysmal nocturnal hematuria (PNH), or insufficient laboratory, pathology, and treatment data. Thirty-one manuscripts were considered after initial abstract and title review. Twenty-four manuscripts, comprising a total of 26 cases, met inclusion criteria. Seven manuscripts were excluded: three had insufficient data, two described pure red cell aplasia on review of full text, one had concomitant diagnosis of PNH, and one was a duplicate case report. Demographic data such as the year published, age, sex, and additional clinical data about laboratory examination, pathologic diagnosis, and surgical and medical management was obtained after thorough review of the manuscript. Response to therapy was defined as the normalization (complete response; CR) or significant improvement (partial response; PR) of hemoglobin, leukocyte, and platelet count.

Results

Case

A 68-year-old Caucasian woman with the past medical history of papillary thyroid cancer treated with thyroidectomy presented to the emergency room with fatigue and cough of about 8–10 weeks duration. She was found to have pancytopenia on a routine complete blood count where the hemoglobin was 7.9 g/dL (normal 12–15.5 g/dL), leukocyte count was $2.0\times10^3/\mu L$ (normal $3.5–10.5\times10^3/\mu L$), absolute neutrophil count was $0.49\times10^9/L$ (normal 1.7–7.0 $10^9/L$), and platelet count was $17\times10^9/L$ (normal $150–450\times10^9/L$). Peripheral smear demonstrated occasional circulating blasts and atypical monocytes. Total bilirubin and creatinine were normal at 0.5 (normal 0.1–1.0 mg/dL) and 0.8 (normal 0.6–1.1 mg/dL), respectively. Evaluation for vitamin B_{12}, folate, thyroid-stimulating hormone, and copper level was unremarkable. Ferritin was elevated at 780 μg/L (11–307 μg/L), and heavy metal screen for arsenic, lead, and mercury was negative in serum. Flow cytometry for PNH demonstrated only 0.05 % of granulocytes with the PNH phenotype. Testing for hepatitis virus A, B, and C, and human immunodeficiency virus 1 and 2, was negative by serology. Polymerase chain reaction assay for cytomegalovirus, Epstein-Barr virus, and parvovirus was negative in serum. Anti-nuclear antibody was mildly positive at 2.0 U (normal <0.1 U). Testing for other autoimmune serology including anti-cyclic citrullinated peptide, anti-Smith, anti-SSA, anti-SSB, anti-Jo, anti-Scl70, and anti-RNP was negative. She had not initiated any new over-the-counter or prescribed medication. Bone marrow biopsy was performed; it demonstrated slightly hypocellular marrow with moderately decreased granulopoiesis, slightly decreased erythropoiesis, and normal to slightly decreased megakaryopoiesis (Fig. 1). It also revealed small lymphoid aggregates containing CD3+/CD8+ lymphocytes admixed with CD19+ lymphocytes. There were no morphologic or immunophenotypic features diagnostic of dysplasia or malignant neoplasm. Cytogenetic studies performed on bone marrow cells revealed normal karyotype (46, XY). She was discharged from the hospital following treatment for neutropenic fever. A bone marrow biopsy was repeated 2 weeks after initial presentation and findings remained unchanged. Flow cytometry on peripheral blood revealed normal quantities of CD3+, CD19+, CD3+/CD4, and CD3+/CD8 positive cells.

Paraneoplastic syndrome was considered in the differential diagnosis, and hence, she underwent CT scan of the chest, abdomen, and pelvis. It revealed a 3.1-cm cystic lesion in the anterior mediastinum (Fig. 2), bilateral pleural effusions, and right adnexal cystic lesion. PET-CT scan showed a hypermetabolic anterior mediastinal mass suspicious for malignancy (Fig. 3). She underwent CT-guided needle biopsy of the anterior mediastinal mass which confirmed this to be a thymoma. She was started on prednisone 1 mg/kg/day and granulocyte colony-stimulating factor (G-CSF) 300 mcg/day without any response. Two weeks later, cyclosporine at 5 mg/kg/day was started and adjusted according to her serum cyclosporine levels to keep it between 150 and 200 ng/mL. In 2 weeks, her laboratory parameters improved (Hgb 10.7 g/dL, leukocyte count $11.9\times10^9/L$, ANC $8.69\times10^9/L$, platelet count $121\times10^9/L$) and she underwent complete resection of her thymoma with evacuation of her right pleural effusion and random biopsies of her right pleura. Final pathology showed well-encapsulated thymoma, World Health Organization (WHO) type B2 (Fig. 4), forming a nodular mass of $5.8\times3.9\times0.7$ cm. Pleural fluid cytology and pleural biopsies showed no malignant cells. Both prednisone and cyclosporine were discontinued after 3 months of therapy. She remains in

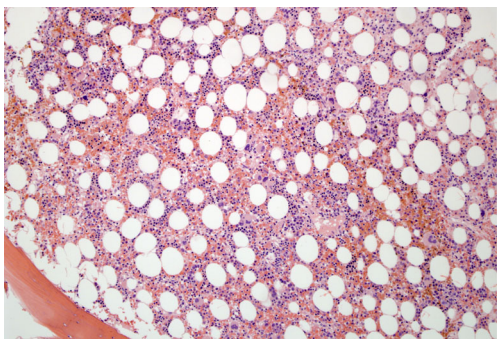

Fig. 1 A photomicrograph of bone marrow biopsy shows slightly hypocellular marrow with moderately decreased granulopoiesis and normal to slightly decreased erythropoiesis and megakaryopoiesis (H&E, ×100)

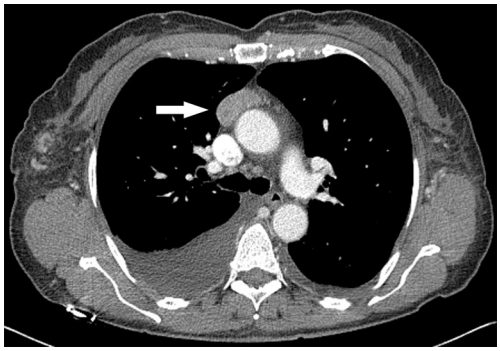

Fig. 2 CT chest showing 3.1×1.5 cm indeterminate low-attenuation lesion (*arrow*) in the anterior mediastinum

complete hematologic remission 7 months following cessation of therapy.

Literature review

A total of 24 manuscripts were included after the inclusion and exclusion criteria were applied. The manuscripts were published between 1958 and 2013. The total cases included in the analysis were 27, of which 26 were obtained from 24 manuscripts [3–27] and the case presented in this manuscript. There were 14 (51.8 %) females and 12 (44.4 %) males; one manuscript did not mention the sex of the patient. The median age of the cohort was 59 years. Median follow-up was 13 months.

All except for one patient had a bone marrow examination performed and was reported to be either hypocellular or aplastic. The median hemoglobin was 6.25 g/dL (range 11.8–3.3 g/dL). The median leukocyte count was 2.45×10^9/L (range 0.5–12.5×10^9/L). The median ANC was 0.8×10^9/L (range 0–4.3×10^9/L). The median platelet count was 12×10^9/L (range 190–2×10^9/L). There were five cases that did not have documented pancytopenia, either due to missing data or normal values. However, all of these patients demonstrated bone marrow aplasia and hence were included. Similarly, in one case [24] where no bone marrow biopsy was reported, pancytopenia (Hgb 6.3 g/dL, leukocyte count 1.1×10^9/L, and platelet count 36×10^9/L) was documented.

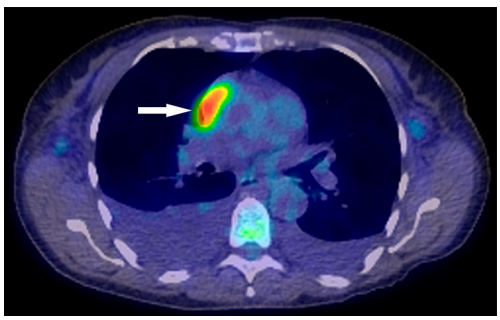

Fig. 3 NMPET/CT scan showing hypermetabolic anterior mediastinal mass (*arrow*) suspicious for malignancy

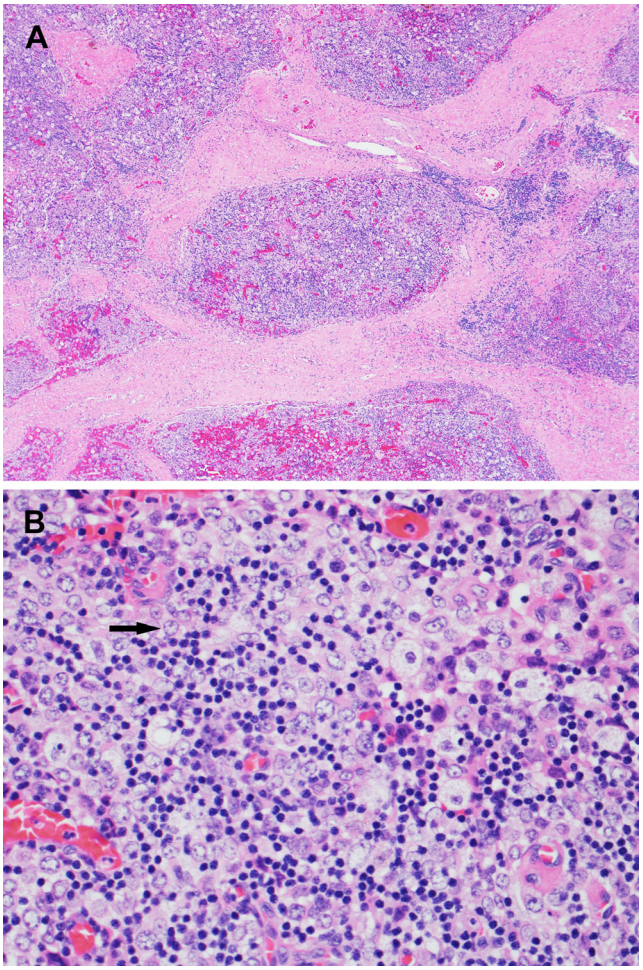

Fig. 4 **a** Low-power photomicrograph of the thymic mass shows a lobulated neoplasm dissected by bands of fibrosis (H&E, ×40). **b** At higher power, the tumor lobules comprised large polygonal epithelial cells with large nuclei, open chromatin, and distinct nucleoli (*arrow*) admixed with small benign lymphocytes (H&E, ×400)

Fatigue (n=11), dyspnea (n=9), and petechial rash/bleeding (n=9) were the most common symptoms. Cough (n=5), which is sometimes associated with thymoma, was not commonly reported. Only three patients reported associated autoimmune phenomena where one had Hashimoto thyroiditis and two had myasthenia gravis. WHO grade and histologic type were not consistently reported (data not shown). However, most patients (n=13) had modified Masaoka stage I (well encapsulated) thymoma on pathologic staging, two had locally invasive disease, and two had metastatic stage IV disease.

Seventeen patients (62.9 %) underwent surgery to remove the thymoma, and there were no reported surgical complications. Two patients received cyclosporine-based treatment before surgical resection. In the remaining 15 patients, pancytopenia either presented after resection of the thymoma (n=6) or was refractory to surgery (n=9). The median time to presentation in the six patients who presented after thymic resection was 20 months (range 6–36 months).

None of the cases published before 1972 (n=9) received cyclosporine or anti-thymocyte globulin (ATG), and all of them expired secondary to either hemorrhage (n=1) or septic shock (n=8). After 1980, when cyclosporine was first used [28], 15 out of 18 remaining patients received cyclosporine. The duration of therapy was not consistently reported. Ten of these 15 patients responded to cyclosporine-based therapy (response rate (RR) 66.6 %; 8 CR and 2 PR). Cyclosporine (n=15) and corticosteroids (n=16) were the most common drugs prescribed for medical management, either alone or in combination with another drug. ATG was also used frequently (n=8) but always in combination with prednisone, cyclosporine, or cyclophosphamide. Two patients underwent allogenic hematopoietic stem cell transplant, one for refractory disease and one for metastatic thymoma. Six patients received external beam radiation, likely with an intention of local control. Three patients received combination chemotherapy regimens, one each for refractory pancytopenia, unresectable locally aggressive disease, and metastatic disease (Table 1).

Discussion

Management of thymoma involves surgical resection, and they generally have good prognosis except for WHO grade C thymic carcinomas. Despite the good prognosis, associated autoimmune syndromes often complicate the clinical management of thymomas. They can be commonly involved with paraneoplastic immunologic phenomena such as myasthenia gravis and pure red cell aplasia. Approximately 25–30 % of

Table 1 Literature review on 27 cases obtained from 25 manuscripts including the present study

Report	Age (years)/ sex	Anemia/leukopenia/ thrombocytopenia	Bone marrow aplasia	Masaoka stage	Surgery	Radiation	Outcome
Green 1958 [7]	78/M	+/−/na	Yes	1	No	No	Died
Green 1958 [7]	70/F	+/+/+	Yes	1	No	10 Gy	Died
Josse and Zacks 1958 [12]	73/F	+/+/+	Yes	1	No	No	Died
Barnes and O'Gorman 1962 [5]	41/M	+/+/+	Yes	2b	No	No	Died
Korn et al. 1967 [14]	75/M	+/+/−	Yes	1	Yes	No	Died
Rogers et al. 1968 [18]	60/F	+/+/+	Yes	1	Yes	No	Died
Talerman and Amigo 1968 [19]	5/M	+/+/na	Yes	1	Yes	No	Died
Burrows and Carroll 1971 [9]	90/M	+/+/+	Yes	na	No	No	Died
Dawson 1972 [10]	18/F	+/+/+	Yes	na	No	44 Gy	Died
Thomas and Manivel 1987 [27]	59/M	+/+/+	Yes	Invasive	No	Yes	Refractory
Lyonnais 1988 [16]	38/na	+/+/+	Yes	1	Yes	No	Resolved
Kobayashi et al. 1993 [13]	59/F	+/+/+	Yes	Invasive	Yes	50 Gy	Resolved
De Gaicomo et al. 1995 [11]	43/F	+/+/+	Yes	1	Yes	No	Resolved
Liozon et al. 1998 [23]	65/M	+/−/+	Yes	1	Yes	No	Refractory
Coplu et al. 2000 [20]	45/F	+/+/+	Yes	1	Yes	No	Resolved
Dincol et al. 2000 [21]	38/M	+/+/+	Yes	1	Yes	No	Resolved
Ritchie et al. 2002 [8]	50/M	+/+/+	Yes	3	Yes	Yes	Resolved
Park et al. 2003 [25]	60/F	+/+/+	Yes	1	Yes	No	Resolved
Trisal et al. 2007 [26]	44/M	+/+/+	Yes	na	Yes	No	Resolved
Arcasoy and Gockerman 2007 [3]	47/F	na	Yes	na	No	No	Died
Gaglia et al. 2007 [22]	68/F	+/+/+	Yes	4a	No	No	Resolved but died
Bajel et al. 2009 [4]	67/M	+/+/+	Yes	na	Yes	No	Resolved
Nakamura et al. 2009 [24]	74/F	+/+/+	No	1	Yes	No	Resolved
Castro et al. 2011 [6]	59/F	+/+/+	Yes	na	Yes	Yes	Died
Castro et al. 2011 [6]	69/M	+/+/+	Yes	na	Yes	No	Resolved
Lu et al. 2013 [15]	40/F	+/+/+	Yes	4b	No	No	Resolved
Present case	68/F	+/+/+	Yes	1	Yes	No	Resolved

na not available, + present, − absent

patients with thymoma will have concomitant myasthenia gravis, and a smaller percentage (approximately 2–5 %) will have pure red cell aplasia. There are numerous other rare paraneoplastic phenomena including pancytopenia, hypogammaglobulinemia, and autoimmune encephalitis. A small number of cases found in this literature review point to a very low incidence of pancytopenia as a complication. The autoimmune paraneoplastic syndromes associated with thymoma are believed to be related to dysregulated T cell immunity. It is not known why some phenomena such as myasthenia gravis are more common than others. The pathogenesis likely involves B cells and autoantibodies [29, 30]. The most common hematologic complication associated with thymoma is pure red cell aplasia where antibodies target a red cell progenitor as shown by serum studies [31]. Other mechanisms such as direct T cell-mediated damage have been postulated in pure red cell aplasia [29]. In most of the cases reported here, the absolute lymphocyte count was normal when reported (data not shown). We could speculate that the pancytopenia is a result of a process which targets a myeloid progenitor cell, resulting in low platelet count, low granulocyte count, and anemia.

Pancytopenia associated with thymoma is a rare entity, and it is unknown whether surgical resection could result in remission. Of all the cases reviewed in this report, none achieved remission with surgery alone. Fifteen of these patients were either refractory to surgical resection or were diagnosed with pancytopenia after resection of thymoma. This suggests that the pancytopenia, which presents as a paraneoplastic syndrome secondary to thymoma, is mostly refractory to surgical resection and can present even after thymectomy. This refractoriness to surgery was previously reported in pure red cell aplasia as well as myasthenia gravis associated with thymoma [32, 33]. Similar to pancytopenia, both these paraneoplastic syndromes can present months after surgical resection of thymoma [34, 35].

In earlier studies, the presence of a paraneoplastic syndrome was considered to be a poor prognostic factor for survival [36–38]. Contrary to this, a recent large retrospective cohort of thymoma patients showed that age, Masaoka stage (stage III and IV), and the presence of thymic carcinoma are the only predictors of overall survival in multivariate analysis [39]. Another large Japanese cohort showed that myasthenia gravis did not affect the overall survival negatively [39, 40]. In the cohort presented here, the most frequent cause of death was infection and subsequent septic shock. It is interesting to note that most deaths were before 1980, whereas there were only three reported deaths after this time. One death was from diffuse alveolar hemorrhage and two from metastatic disease. This difference could be due to availability of cyclosporine alone and/or better supportive care and antimicrobials. There is of course a possibility of strong publication bias, and some cases still probably go undiagnosed and unreported.

All nine patients before 1980 were treated with corticosteroids, testosterone, or adrenocorticotropic hormone. All of them died secondary to complications from pancytopenia. Four of these nine patients had thymectomy, but none resulted in resolution of pancytopenia. Cyclosporine-based therapy showed a response rate of 66.6 % in the cohort presented in this manuscript. Other than corticosteroids, cyclosporine was the most commonly used drug, either alone or in combination with other agents such as ATG, G-CSF, tacrolimus, or mycophenolate mofetil. Combination immunosuppressive therapy was generally used in refractory cases. This is a small number of cases to make any definitive conclusion about which combination is more effective or if any drug can be used alone successfully. It is clear though that single-agent therapy with corticosteroids is ineffective. Randomized clinical trials are likely not feasible in such a rare disorder. What is not clear from these past reports is how long the immunosuppressive therapy is needed, and what characterizes the refractory cases?

In conclusion, our report for the first time has compiled all cases of pancytopenia associated with thymoma from the current literature. The data presented herein suggest that surgical resection does not result in resolution of pancytopenia and medical management is often required. A careful multidisciplinary approach to treatment is needed in all of these cases, but if medical treatment is required, strong consideration should be given to cyclosporine-based treatment.

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Conflict of interest The authors declare that they have no conflict of interest.

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