Case Report

Thymoma with Granulomatous Myositis, Pure Red Cell Aplasia, and Hepatosplenomegaly: A Case Report and Review Literature

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Background: *Thymoma is well-recognized as being associated with various autoimmune diseases. Thymoma associated with granulomatous myositis (GM) is rare and thymoma associated with pure red cell aplasia (PRCA) is somewhat more frequent. However, coexistence of GM and PRCA in a thymoma patient is extremely uncommon.*
Case Report: *Here, we present the case of a 40-year-old Thai male who presented with progressive proximal muscle weakness with dysphagia, anemia, hepatosplenomegaly, and an anterior mediastinal mass. After a thorough investigation, the patient was diagnosed with stage I type AB thymoma with GM and PRCA. Following treatment with thymectomy, corticosteroids, and immunosuppressive agents, muscle weakness improved, hepatosplenomegaly resolved, and laboratory abnormalities normalized. The patient was then able to resume his normal daily activities and return to work.*
Conclusion: *In this case, we report a rare association of GM, PRCA, hepatosplenomegaly, and thymoma. Early detection with prompt treatment with tumor removal and immunosuppressive medications resulted in a good clinical response. Based on our review of the literature, this is the first published case report to describe this combination of coexisting conditions.*

Keywords: *Thymoma, Granulomatous myositis, Pure red cell aplasia, Hepatosplenomegaly, Paraneoplastic syndrome*

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Thymoma, a tumor originating from epithelial cells in the thymus, typically occurs in adults 40 to 70 years of age[1]. It is well-recognized as being associated with various paraneoplastic syndromes. The symptoms of associated paraneoplastic syndromes may be the first clinical presentation and can affect diverse organ systems, most notably the neurologic, rheumatologic, and hematologic systems[2-4]. Myasthenia gravis (MG) is the most common of the paraneoplastic syndromes in patient who have thymoma[2]. Granulomatous myositis (GM) associated with thymoma is rare. The association of pure red cell aplasia (PRCA) with thymoma is more common than GM associated with thymoma[4], but coexistence of GM and PRCA in a thymoma patient has not been previously reported. Here, we present an unusual association of thymoma with GM, PRCA, and hepatosplenomegaly with good response to a combination treatment strategy of surgical resection and immunosuppressive therapy.

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Case Report

A 40-year-old Thai male presented with low-grade fever, dysphagia, proximal muscle weakness without diurnal variation, and significant weight loss over three months. He had no remarkable past medical or family history. Significant findings from physical examination were a fever of 38°C, moderate pallor, and hepatosplenomegaly. Generalized muscle wasting and symmetrical proximal muscle weakness was noted, with normal deep tendon reflex and sensation.

Laboratory findings included an elevated serum creatine phosphokinase (CPK) of 9,259 U/L (0 to 190), lactate dehydrogenase of 1,807 U/L (240 to 480),

aspartate aminotransferase of 528 U/L (0 to 40), and alanine aminotransferase of 493 U/L (0 to 40). Serum electrolytes and thyroid function tests were normal, and anti-HIV antibodies were negative. Electromyography (EMG) showed signs of membrane instability, fibrillation, positive sharp wave, and small polyphasic short duration motor unit action potentials in the right gluteus medius, left deltoid, and thoracic paraspinal muscles, which were compatible with a myopathic pattern. Serum antinuclear antibody titer was 1:320 with homogeneous, fine-speckled, and nucleolar pattern, and no anti-synthetase, anti-signal recognition particle, or anti-Mi2 were identified. Based on these findings, a diagnosis of polymyositis was made.

Additional studies to investigate for related conditions were conducted, which identified an anterior mediastinal mass on chest X-ray (Fig. 1A). Computed tomography (CT) of the chest with contrast revealed a well-defined, homogeneous, enhancing, soft tissue mass in the left anterior mediastinum (Fig. 1B). Abdominal CT with contrast revealed hepatosplenomegaly without space-occupying lesions. In addition, multiple enlarged intra-abdominal lymph nodes were observed that were up to 1.1 cm in size. Due to the presence of hepatosplenomegaly and diffuse lymphadenopathy, myositis associated with lymphoma was the initial presumed diagnosis. Transcutaneous core needle biopsy of the anterior mediastinal mass was performed, which revealed type B2 thymoma (2004 WHO classification). Thymectomy was performed and histopathologic examination revealed type AB (mixed) thymoma of 8.0x6.7x4.0 cm, with no capsular or vascular invasion. No evidence of lymphoma was observed. Quadriceps muscle biopsy was performed prior to thymectomy, which revealed non-caseous granulomatous inflammation with epithelioid cells and multinucleated cells resulting in a diagnosis of GM. Enzyme histochemistry and immunohistochemistry were positive for acid phosphatase staining macrophages and CD68 positive multinucleated cells (Fig. 2). Additional immunohistochemistry for CD4 and CD8 lymphocytes were performed, which showed a small number of CD4 positive lymphocytes in the granuloma and perivascular area, while CD8 positive lymphocytes were detected only in the granuloma. Acid-fast bacillus and Gomori methenamine silver (GMS) stains for mycobacterial and fungal infection were negative.

Concurrent to the evaluation of the mediastinal mass, a number of hematologic abnormalities were noted an investigated. Complete blood count revealed hemoglobin (Hb) of 8 g/dl, hematocrit of 24.1%, and absolute reticulocyte count of 3,000/µl, with normal white cell and platelet counts. Bone marrow aspiration showed decreased erythroid precursors (<1% of cellularity). Bone marrow biopsy revealed mildly hypocellular trilineage marrow, markedly decreased erythroid precursors, no abnormal lymphocytes, and mildly increased megakaryocytes which were compatible with PRCA.

Based on the above findings, the final diagnosis in our presented case was stage I thymoma type AB with PRCA and GM. The patient was treated with chloroquine 250 mg/day orally and dexamethasone 20 mg/day intravenously. Muscle strength and dysphagia improved within seven days. After three weeks of

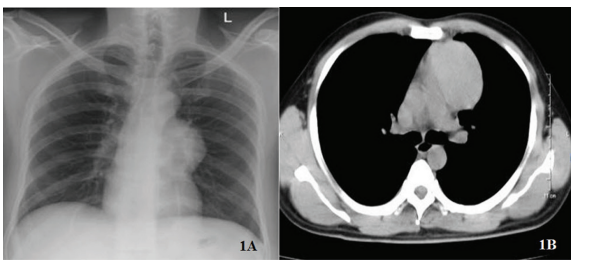

Fig. 1 A) Chest radiograph showed an anterior mediastinal mass. B) Chest CT showed a soft tissue mass with well-defined smooth border, oval shape, and homogeneous enhancement, measuring 8x7x5 cm in the left anterior mediastinum.

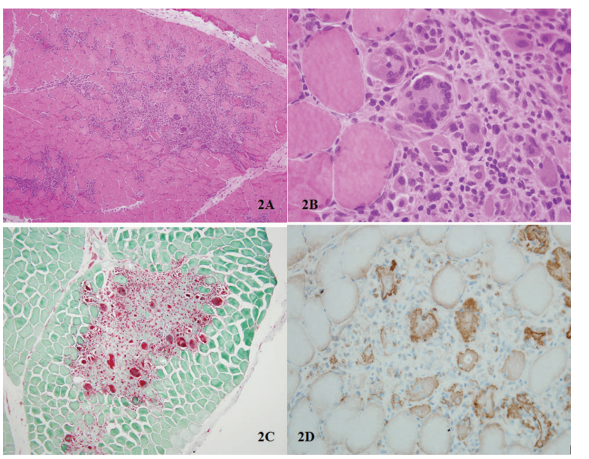

Fig. 2 Quadriceps muscle biopsy revealed: A) multi-foci of inflammatory cells in endomysial area (H&E, 20x), B) non-caseous granulomatous inflammation with epithelioid cells and multinucleated cells (H&E, 400x), C) positive staining for acid phosphatase in macrophages (100x), D) positive staining for CD68 in multinucleated cells (200x).

treatment, serum CPK returned to normal, while Hb was increased to 10.5 g/dl. Dexamethasone was then changed to prednisolone 50 mg/day orally and chloroquine 250 mg/day was continued. Azathioprine 100 mg/day orally was added as a steroid-sparing agent. After 3 months of treatment the prednisolone had been tapered down to 15 mg/day. Muscle strength returned to normal, while Hb increased to 13.9 g/dl without blood transfusion. The patient was able to resume his daily activities and return to work. Hepatosplenomegaly was improved after a few weeks of treatment on physical examination. Abdominal CT, six months after treatment completion, confirmed a normal sized liver and spleen with no significant lymphadenopathy. At the 1-year follow-up, our patient remained in remission and continues on azathioprine 100 mg/day and chloroquine 125 mg/day.

Discussion

Thymoma is the most common primary tumor in the anterior mediastinum[5]. It is frequently associated with immune- and non-immune-mediated paraneoplastic syndromes. In up to 50% of cases, thymoma has been reported to have two synchronous paraneoplastic syndromes[6]. While multiple concurrent paraneoplastic syndromes are common, GM and PRCA have not been reported together. GM is a rare condition with identify in 0.5% of 2,985 muscle biopsy specimens[7] and is most frequently associated with sarcoidosis[8]. GM associated with thymoma is extremely rare. Previous reports of GM associated with histology-confirmed thymoma[9-12] are shown in Table 1. GM can develop before or after thymectomy[10,12], and the pathogenesis is still unknown. Similar to reports by Herrmann et al[10] and Jasim and Shaibani[12], our patient's EMG revealed a myopathic pattern with inflammation, but our patient had constitutional symptoms that were dissimilar to those two cases. Approximately 2 to 5% of patients who have PRCA are observed to have thymoma[13] and less than 10% of patients with thymoma developed PRCA[4]. However, it is the second most common paraneoplastic syndrome associated with thymoma following MG. Our review of the literature revealed few reports of concomitant hepatosplenomegaly and thymoma. These cases were mostly concurrent with lymphoma, liver metastasis from thymic carcinoma, or another secondary malignancy. In the present case, we extensively investigated the etiology of hepatosplenomegaly, but we were not able to identify other causes. Given the fact that it resolved with treatment of underlying thymoma, we believe the two are likely related.

Treatment of GM associated with thymoma is not well-established. Given that GM is likely to be a paraneoplastic disease, elimination of the underlying malignancy is the mainstay of treatment[11]. In addition

Table 1. Characteristics, treatment, and outcome of five patients with granulomatous myositis associated with thymoma

	Present case	Namba, et al.[9]	Herrmann, et al.[10]	Schädel, et al.[11]	Jasim, et al.[12]
Age (years)/gender	40/male	69/female	56/male	64/male	59/male
Duration of muscle symptom	3 months	6 months	18 months	N/A	3 weeks
Dysphagia	Yes	N/A	Yes	Yes	Yes
CPK (U/L)	9,259 (<190)	N/A	728 (<240)	735 (NA)	1,096 (<250)
Thymoma	Benign	Benign	Benign	Metastatic	N/A
Associated condition/disease	PRCA, hepato splenomegaly	MG, giant cell myocarditis	Biliary cirrhosis, pancytopenia	MG	MG
Corticosteroid treatment	Yes	N/A	Yes	Yes	Yes
Immunosuppressive drug	Azathioprine 100 mg/day	N/A	IVIg 2g, followed by 1 gm/month for 3 months	Cisplatin, doxorubicin, cyclophosphamide	Azathioprine 200 mg/day
Outcome	Rapid response; clinical remission within 3 months	N/A	Improve after 3 months	Rapid response only muscle symptoms, decreased tumor size; flare after 2 months then initiating cyclo-phosphamide and significantly improved both muscle symptom and dysphagia	Rapid response; clinical remission within 3 months

CPK = serum creatine phosphokinase; PRCA = pure red cell aplasia; MG = myasthenia gravis; N/A = data not available

to thymectomy, high-dose corticosteroid was given in all previously reported cases with various responses noted[10,12]. Similar to the patient reported by Jasim and Shaibani[12], our patient responded well to a combination of high-dose corticosteroid and azathioprine. The optimal treatment for PRCA associated with thymoma is also unclear. Thymectomy alone leads to remission of PRCA in 25 to 30% of cases[14]. A recently published study from Japan reported a complete remission rate of 95% with cyclosporine when used as a first-line therapy in patients with thymoma-associated PRCA[15]. Information regarding the efficacy of cytotoxic drugs (cyclophosphamide, cyclosporine, azathioprine, and methotrexate) for treatment of GM and PRCA when associated with thymoma is scarce; however, these agents are generally considered to be appropriate alternatives in patients with corticosteroid-induced side effects or lack of response to corticosteroids[6].

Conclusion

We report a rare association of GM, PRCA, hepatosplenomegaly, and thymoma. Early detection with prompt treatment and tumor removal with corticosteroid and immunosuppressive medications resulted in resolution of all three syndromes. Based on our review of the literature, this is the first published case report to describe this combination of coexisting conditions.

What is already known on this topic?

1. Thymoma is the most common anterior mediastinal tumor, which is commonly associated with various autoimmune diseases.
2. GM is a rare condition that is most frequently associated with sarcoidosis. GM associated with thymoma is extremely rare.
3. Association of PRCA with thymoma commonly found in thymoma patients.
4. Coexistence of GM and PRCA in a thymoma patient has not been previously reported.

What this study adds?

This study reports a rare case of thymoma associated with GM, PRCA, and hepatosplenomegaly. There are no standard treatments for these conditions when occurring concurrently. Clinicians should consider the diagnosis of GM in patients presenting with thymoma and muscle weakness. Early detection with prompt treatment and tumor removal with corticosteroid and immunosuppressive medications resulted in a good clinical response despite having multiple concurrent associated syndromes. This is the first published case report to describe this combination of coexisting conditions.

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Potential conflicts of interest

None.

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เนื้องอกต่อมไทมัสกับกล้ามเนื้ออักเสบชนิด granuloma ภาวะไขกระดูกไม่สร้างเม็ดเลือดแดง และตับม้ามโต: รายงานผู้ป่วย 1 ราย และทบทวนวรรณกรรม

กฤติยา กอไพศาล, ธนวรรณ อภิบุณโยภาส, ฉัตรี หาญทวีพันธุ์, ตุ้มทิพย์ แสงรุจี, วราลักษณ์ ศรีนนท์ประเสริฐ, ปวีณา เชี่ยวชาญวิศวกิจ

ภูมิหลัง: *เป็นที่รู้จักกันดีว่าเนื้องอกต่อมไทมัสเกิดร่วมกับภาวะกลุ่มโรคภูมิคุ้มกันทำร้ายตัวเองได้หลายชนิด เนื้องอกต่อมไทมัสพบร่วมกับกล้ามเนื้ออักเสบชนิด granuloma ได้น้อยมาก เนื้องอกต่อมไทมัสพบร่วมกับภาวะไขกระดูกไม่สร้างเม็ดเลือดแดงพบได้มากกว่า อย่างไรก็ตามไม่เคยพบการเกิดเนื้องอกต่อมไทมัสที่พบร่วมกับกล้ามเนื้ออักเสบชนิด granuloma และภาวะไขกระดูกไม่สร้างเม็ดเลือดแดงพร้อมกัน*

รายงานผู้ป่วย: *ชายไทยอายุ 40 ปี มาด้วยอาการอ่อนแรงกล้ามเนื้อส่วนต้น กลืนลำบาก ซีด ตับม้ามโต และพบก้อนที่เมดิแอสตินัมส่วนหน้า หลังจากตรวจผู้ป่วยได้รับการวินิจฉัยว่าเป็นเนื้องอกไทมัสระยะที่ 1 ชนิด AB ร่วมกับมีกลุ่มอาการ กล้ามเนื้ออักเสบชนิด granuloma ภาวะไขกระดูกไม่สร้างเม็ดเลือดแดง และตับม้ามโต หลังจากการรักษาด้วยการผ่าตัดต่อมไทมัส ให้สเตียรอยด์ และยากดภูมิคุ้มกัน อาการอ่อนแรงดีขึ้น ไม่พบตับม้ามโต และค่าทางห้องปฏิบัติการกลับมาปกติ ผู้ป่วยสามารถกลับไปทำกิจวัตรประจำวันและทำงานได้ปกติ*

สรุป: *รายงานผู้ป่วยที่เป็นเนื้องอกต่อมไทมัสพบร่วมกับกล้ามเนื้ออักเสบชนิด granuloma ภาวะไขกระดูกไม่สร้างเม็ดเลือดแดง และตับม้ามโต การวินิจฉัยได้อย่างรวดเร็วร่วมกับรักษาด้วยการผ่าตัดต่อมไทมัส และการให้ยากดภูมิคุ้มกันตั้งแต่ช่วงแรก นำไปสู่ผลการรักษาที่ดี จากการทบทวนวรรณกรรมที่ผ่านมา รายงานนี้คือการรายงานผู้ป่วยครั้งแรกที่อธิบายถึงความสัมพันธ์ดังกล่าว*