Rare paraneoplastic aplastic anemia in malignant thymoma patient: a case report

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Abstract

Aplastic anemia, a rare immune-mediated complication, presented as pancytopenia was described in a patient with malignant thymoma. It may present together with, or prior to, tumor diagnosis or occur after tumor resection. Immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation is required. In this report, we present the case of a 38-year-old man with an inoperable type B1 thymoma who developed prolonged pancytopenia after two cycles of palliative chemotherapy. Bone marrow biopsy was carried out and severe aplastic anemia was established. The patient was unsuccessfully treated with anti-thymocyte globulin plus cyclosporine. Difficulty in treating remains a problem. Further studies are needed to determine the proper treatment plan.

Keywords: Aplastic anemia, thymoma, anti-thymocyte globulin, cyclosporine, prognosis

ภาวะไขกระดูกฝ่อที่เกี่ยวข้องกับเนื้องอกร้ายของต่อมไทมัส: รายงานผู้ป่วย

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บทคัดย่อ

ภาวะไขกระดูกฝ่อ ที่เกิดจากความผิดปกติทางภูมิคุ้มกันที่เกี่ยวข้องกับเนื้องอกร้ายของต่อมไทมัส เป็นภาวะพบได้ไม่บ่อย โดยตรวจเลือดพบว่ามีจำนวนเม็ดเลือดแดง เม็ดเลือดขาว และเกร็ดเลือดต่ำกว่าปกติ ภาวะไขกระดูกฝ่อที่เกี่ยวข้องกับเนื้องอกร้ายของต่อมไทมัสอาจเกิดขึ้นก่อนที่จะตรวจพบก้อนเนื้องอกของต่อมไทมัส พร้อมกัน หรือเกิดตามหลังจากที่ได้รับการรักษาต่อมไทมัสโดยการผ่าตัดต่อมไทมัสออกไปแล้วก็ได้ แนวทางการรักษาในปัจจุบัน ได้แก่ การรักษาด้วยยากดภูมิคุ้มกัน หรือการรักษาด้วยการปลูกถ่ายไขกระดูก เป็นต้น รายงานฉบับนี้เป็นรายงานกรณีผู้ป่วยชาย อายุ 38 ปี ซึ่งได้รับการวินิจฉัยเป็นเนื้องอกต่อมไทมัสชนิดบีหนึ่ง และเป็นระยะที่ผ่าตัดไม่ได้ จึงได้รับการรักษาด้วยยาเคมีบำบัด ภายหลังได้รับยาเคมีบำบัด 2 รอบ ผู้ป่วยตรวจเลือดพบว่ามีภาวะเม็ดเลือดแดง เม็ดเลือดขาว และเกร็ดเลือดต่ำ ซึ่งเป็นอยู่ต่อเนื่องนานกว่าปกติ จึงได้รับการเจาะตรวจไขกระดูกซึ่งผลเข้าได้กับภาวะไขกระดูกฝ่อ ผู้ป่วยได้รับการรักษาด้วยยากดภูมิคุ้มกัน anti-thymocyte globulin และ cyclosporin แต่การรักษาไม่ประสบความสำเร็จ ในปัจจุบัน ความยากในการรักษาภาวะไขกระดูกฝ่อที่เกี่ยวข้องกับเนื้องอกร้ายของต่อมไทมัสนี้ให้หายขาดยังเป็นปัญหาอยู่ ดังนั้นการศึกษาวิจัยเพิ่มเติมเกี่ยวกับภาวะนี้ จึงเป็นสิ่งจำเป็นและมีความสำคัญเพื่อให้ได้การรักษาที่เหมาะสมและดียิ่งขึ้น

Introduction

Malignant thymoma is an uncommon tumor in Thailand which is associated with many paraneoplastic diseases, including myasthenia gravis, pure red cell aplasia (PRCA), hypogammaglobulinemia and aplastic anemia[1]. Aplastic anemia is a rare autoimmune-mediated complication of malignant thymoma, which occurs in 1% of cases[2] and is a reason for discontinuing chemotherapy. Its pathogenesis has been postulated via self-reactive T-cell clones generated by thymic epithelium[3]. Immunosuppressive therapy is required for producing hematologic response.[4] This report describes the case of a 38-year-old male with malignant thymoma who presented with prolonged pancytopenia during chemotherapy treatment.

Case report

A 38 year-old male with a background history of fatty liver was diagnosed with progressive dyspnea over the previous 6 months. His chest x-ray revealed homogeneous opacity of the entire right lung (figure 1A). Chest computed tomography (CT) demonstrated a large lobulated enhancing mass at right anterior mediastinum extending to posterior mediastinum, which compressed the superior vena cava. CT also revealed multiple pleural masses with right pleural effusion. Biopsy of pleural mass was performed and was consistent with malignant thymoma type B1. Due to inoperable disease he was offered palliative chemotherapy, which consisted of doxorubicin, cyclophosphamide and cisplatin. After two cycles of chemotherapy, the patient experienced a partial response (figure 1B). The mediastinal mass, pleural mass and pleural effusion demonstrated a significant decrease in size. Unfortunately, he was noted to have an abnormal hematologic test results that limited his receiving the next cycle of chemotherapy. About 2 months after his last chemotherapy, his complete blood count still showed anemia, neutropenia and thrombocytopenia: hemoglobin 5.6 g/dl, WBC 5.7 x 10^9/L, platelet count 7.0 x 10^9/L, WBC differential count with 7 % of polymorphonuclear (PMN) leukocytes, 91% of lymphocytes, and reticulocyte count of 0.2%. His physical examination was only remarkable for pallor and decreased breath sounds along the right lower lung field. Tests for viral hepatitis, HIV and antinuclear antibody were negative. Due to pancytopenia, further chemotherapy was deferred, despite his malignant thymoma responding to treatment. At that time he was sent for octreotide scan (^{99m}Tc-labeled somatostatin analogue, ^{99m}Tc-HYNIC-TOC) and

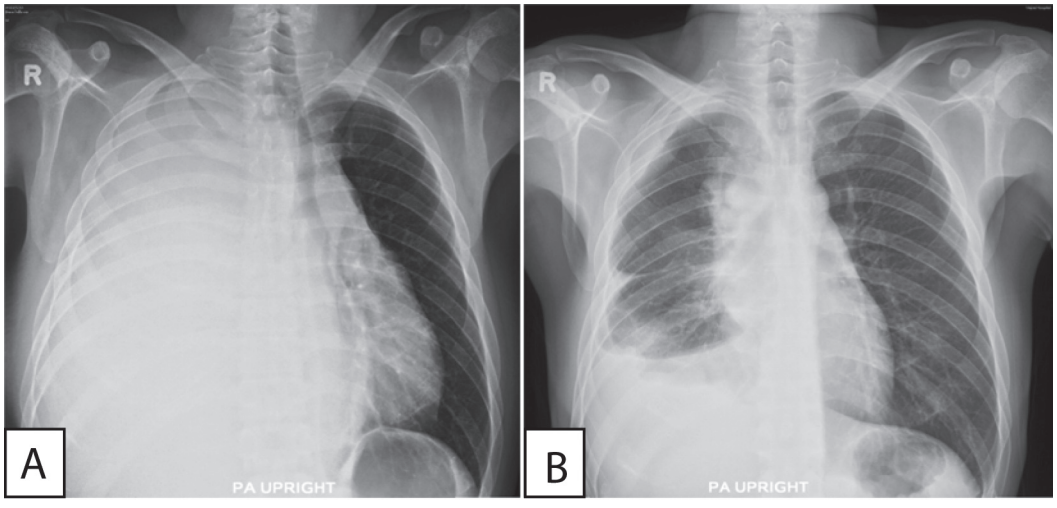


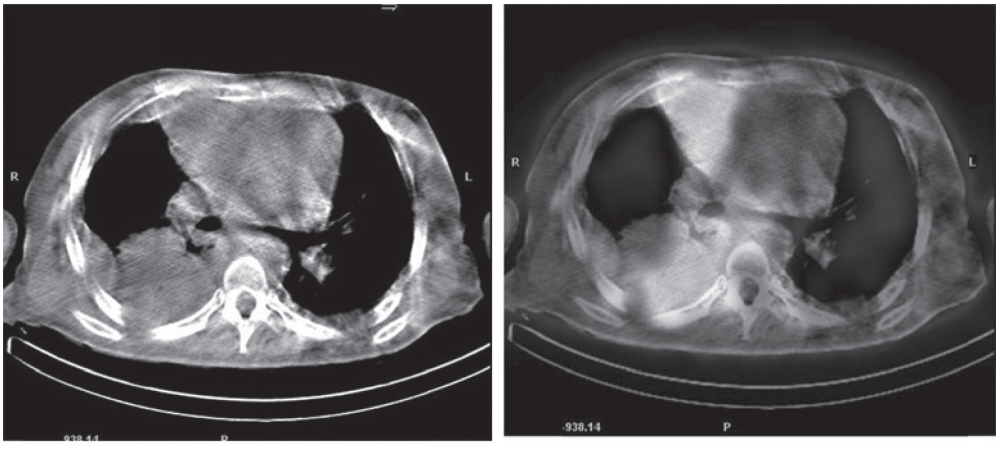
Figure 1: A) Chest X-ray at initial presentation B) Chest X-ray after 2 cycles of chemotherapy

we planned to use octreotide plus prednisolone if the patient developed progressive disease of malignant thymoma. The results demonstrated a radiotracer uptake at right chest and right mediastinal region (figure 2). Additionally, a hematologist was consulted and bone marrow biopsy was carried out. The results showed severely hypocellular trilineage marrow and no evidence of malignant cell involvement. Peripheral blood flow cytometric analysis of all lymphocyte subset panels was evaluated. The result showed an increase in CD8+ T-cells while other subtypes of lymphocytes were decreased. Serum immunoelectrophoresis demonstrated no hypogammaglobulinemia. These results supported the diagnosis of an immune-mediated aplastic anemia. The patient was then treated with antithymocyte globulin (ATG) and cyclosporine. He was prescribed cyclosporine 200 mg twice a day and rabbit ATG 3 mg/kg/day for a 5-day infusion. Short courses of methylprednisolone and antihistamine were added for preventing anaphylaxis during ATG administration. Unfortunately, one month later he developed *Klebsiella pneumoniae* septicemia with seizure due to brain abscess. Pancytopenia had not yet been reversed. The patient eventually had cardiac arrest.

Discussion

Malignant thymoma is classified as type A, B and AB according to the World Health Organization, and associated with paraneoplastic disorders. The most common of which is myasthenia gravis[5]. Here we present the case of a patient who was diagnosed with malignant thymoma type B1 an developed severe aplastic anemia, a rare hematologic paraneoplastic syndrome.

Type B1 thymoma accounts for approximately 20% of all thymomas[6]. The WHO classification of thymoma is clearly associated with the clinical behavior. Type A, AB and B1 thymomas are classified to the low-risk group, type B2 and B3 thymomas are the intermediate group and type C thymoma is the group with the worst prognosis. However, the Masaoka tumor stage is the single most important prognostic factor of thymoma. The median survival time of patients in stage IV was 14 months[7]. In this patient, the survival time was 9 months which was less than expected and this may be due to a hematologic paraneoplastic syndrome. Hematologic function abnormalities such as thrombocytopenia and neutropenia are the limitation for chemotherapy treatment and



Chest computed tomography Octreotide scan (^{99m}Tc-HYNIC-TOC)

Figure 2: Octreotide scan (^{99m}Tc-HYNIC-TOC) reveals abnormal radiotracer uptake in the posterior right chest and right–side mediastinal region that is corresponding with a lesion in chest computed tomography finding.

are associated with increased adverse events, e.g., bleeding and infection. In this case, the patient with malignant thymoma type B1 stage IV had developed a very rare hematologic paraneoplastic syndrome, that is severe aplastic anemia. So we are looking for an effective and non-chemotherapy based therapy that can treat thymoma patients with severe aplastic anemia.

We found one piece of evidence based from an Eastern Cooperative Oncology Group (ECOG) phase II study describing use of octreotide alone or with prednisolone. Octreotide is an octapeptide SST (somatostatin) analog that has a high affinity for a selective SST subtype 2 (SST2) receptor. In human body organs, the thymic epithelial cells seem to be a major site of SST production. The results from the ECOG study showed a response rate of about 30% and revealed that octreotide alone has modest activity in patients with octreotide scan–positive thymoma, and that the addition of prednisone improves the overall response rate but is associated with increased toxicities such as infection without neutropenia, and hyperglycemia[8].

^{111}In- or ^{99m}Tc-labeled somatostatin analogs are receptor-mediated radionuclides that specifically bind with high affinity to SST receptors, especially subtype 2, which is expressed in the normal thymus. Positive for octreotide scan in thymoma indicated that patients who may respond to treatment with octreotide[8].

Aplastic anemia is a rare complication among malignant thymoma patients. It may present together with or prior to tumor diagnosis or occur after tumor resection[3]. It is an autoimmune process, especially well established to relate with auto-reactive T cells and produce clonal T cell expansion was demonstrated among malignant thymoma cells. And it can be explained by increased cytotoxic T-cells/ suppressive cells[3]. In this case, flow cytometry from peripheral blood demonstrated increased CD8+ T-cells consistent with the pathogenesis of his conditions.

The identification of a clonal T-cell population supports the hypothesis that self-reactive T- cells from the thymoma are exported to the periphery causing self-immunity at a later date[3].Thus, surgical resection was generally ineffective for treatment and had no impact on the clinical course of aplastic anemia[3]. According to laboratory findings such as severe hypocellular marrow, profound neutropenia, hyporeticulocytosis and marked thrombocytopenia, severe aplastic anemia was diagnosed. Many treatment guidelines recommend treatment with a human leukocyte antigen matched sibling (HLA sibling) allogeneic hemopoietic stem cell transplantation (AlloHSCT) or immunosuppressive drugs[9] but his condition was not suitable for AlloHSCT. ATG and cyclosporine were prescribed. Approximately 60 % of cases achieve hematologic response after treatment with dual immunosuppressive drugs[10]. But in this case, there was a heterogeneity response; some cases showed remission and some other cases did not achieve hematologic response and progressed to death in a short period. In this case, refractory cytopenia persisted without response, he remained transfusion dependent. He developed gram-negative bacterial septicemia and the patient died due to infectious complication.

In thymoma-associated aplastic anemia, we found a published report of a patient who had undergone HLA sibling alloHSCT after resection of thymoma and achieved excellent response and it seemed to be more durable compared with dual immunosuppressive therapy[10].The challenge of thymoma resection in the case of severe pancytopenia present enormous difficulties[10]. In the future, additional studies in a larger population are needed to confirm this hypothesis and to determine decision-making about treatment of thymoma-associated aplastic anemia.

Conclusion

As documented, malignant thymoma is a chemoresponsive tumor. Despite the risk of metastasis and superior vena cava syndrome, it still shows a good response. However, not all thymoma-associated paraneoplastic autoimmune disease will be cured or improved, even after thymomas

have been removed or decreased in size after treatments. Aplastic anemia, which is a very rare paraneoplastic syndrome and difficult to treat, is one of the prognostic factors associated with poor survival. Treatment of aplastic anemia in malignant thymoma is required and needs further study.

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