A rare association of thymoma and immunodeficiency: Two cases reports

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1.Introduction

In 1954 Robert Good described three patients with thymoma and hypogammaglobulinemia. Today, the condition is designated as Good syndrome [1]. It is typically anadult-onset immunodeficiency rendering patient susceptible to bacterial,opportunisticviral and fungal infections.Hematological disorders and associated autoimmune diseases are also common.

Additional immunologic defects in GS may include altered T-cell function with low CD4 cells, and an inverted ratio of CD4 to CD8 cells. The humoral and cellular immunodeficiency in GS is responsible for recurrent respiratory, gastrointestinaland urinary infections from common pathogens [2].The pathogenesis remains unknown and, what is more, no genetic studies have been reported [3,4].

Optimal therapy often requires perioperative medical immunomodulation and surgical resection. Herein, we describe twocases of thymoma with hypogammaglobulinemia and their clinical and immunological presentation.

2. Case reports:

2.1. Case 1:

A 60 years-old man was referred to Beni Messous teaching hospital of Algiers for the investigation of a mediastinal bulge demonstrated earlier by a chest X- ray. The patient has been healthy until the age of 45, when he developed a pneumococcal chronic otitis. Three years ago, he started to experience recurrent bronchitis.

At presentation, the patient had fever (38.5° C), a super infection of chronic bilateral otitis complicated by a facial palsy, thrush with cutaneous mycosis in the abdomen and both forearms. Chest radiograph revealed an abnormal soft tissue density along the right border of the heart and a bilateral pleural effusion. Pericardial effusion was noted on echocardiography. High-resolution CT scan showed a rounded 65x53x43mm mass, bilateral bronchiectasis **(Fig.1)** infected by *Pseudomonas aeruginosa* and vertebral bodies hemangiomasatD3andD10 **(Fig.2)**. Culture of pleural fluid yielded *Klebsiella pneumoniae.*

Laboratory investigations on admission showed a

hypogammaglobulinemia: IgG 87,6 mg/dL (normal: 800-1600 mg/dL), IgA and IgM were undetectable (normal, respectively: 70-400 mg/dL, 40-230mg/dL). Immunophenotyping of peripheral blood lymphocytes subsets by flow cytometry revealed a total depletion of B CD19+ cells, a low level of T CD4+ and a subsequent reversed T CD4+/ T CD8+ ratio. HIV, HCV and HBV serologies were negative, while testing for CMV came back positive for IgG. The patient was put under antibiotics according to the antibiogram results: ciprofloxacin 400 mg/day and gentamicin 160 mg/ day. An anti- fungal treatment was prescribed for the thrush and the cutaneous mycosis. A cyclic IVIG replacement therapy was instaured at 0.5 g/kg/day every three weeks.

After the otitis and bronchitis symptoms improved, the patient was admitted for surgical removal of the anterior mediastinal mass. Thymectomy was performed; the tumor was labeled type AB upon histological examination, according to the WHO classification. The findings of thymoma and hypogammaglobulinemia were consistent with Good's syndrome, which in this patient was manifested by recurrent sinopulmonary disease. Our patient has not experienced any severe infections since the thymectomy (more than one year). However, surgery did not alleviate the immunodeficiency. Currently, he is still under immunoglobulin replacement therapy.

2.2. Case 2:

A 23-year-old manpatient from unrelated parents. There is no family history of immunodeficiency. He was a lifelong nonsmoker.In the last 6 months prior to current admission,he developed several episodes of respiratory infectionsof the upper and lower tract and watery, bloody diarrhea occurring 5–10 times per day, ultimately leading to a weight loss, requiringantibiotic treatment and hospitalization.The patient underwent an extensive outpatient workup, including testing for infectious etiologies and celiac disease, with all laboratory tests unremarkable.In the report of a general medical laboratory, severely reduced serum immunoglobulin concentration was mentioned.

On physical examination, the patient was a thin. He was apyrexial with a temperature of 36,5°C, but tachycardic withheart rate of 117/min and blood pressure of 104/68 mmHg, SaO_2 of 95% at room air. There were bilateral basal crackles on chest examination. Lymphadenopathy was not noted. The remainder of the examination was unremarkable.

The computed tomography of the chest, abdomen and pelvis showed an anterior mediastinal mass measuring 61×25 mm suggesting thymoma (**Fig. 3)**, Pleural effusion of moderate abundance and excavated pulmonary lesions (**Fig. 4**).

Initial laboratory tests showed the following abnormalities:leukocytosis (16.7 × 10^9/L with 82.9% of polymorphonuclear cells), anemia (Hb 11.7 g/dL) with mean corpuscular volume of 89.2, thrombocytopenia (124× 10^9/L), CRP 39 mg/L. Following blood measures were within the normal ranges: glucose, creatinine, urea, LDH, uric acid, bilirubin, transaminases.

The followings tests were normal or negative: viral serology(HIV, hepatitis B and C), rheumatoid factor, antinuclear antibodies, anti-Cyclic Citrullinated Peptide antibodies, Anti-parietal cell antibodies, Intrinsic Factor Antibodies,anti-neutrophil cytoplasmic antibodies, tumoral antigens. Serum protein electrophoresis demonstrated hypoalbuminemia (25.03g/L), normal concentration of α-1 and α-2 globulins (2,36 g/L, 6,19 g/L respectively) and major hypogammaglobulinemia (3,18 g/L).

Immunological examination revealed the following: low immunoglobulin G (IgG), 277mg/dL (normal: 800-1600 mg/dL); IgA, 85 mg/dL (normal: 70-400 mg/dL); IgM, <0.1 mg/dL (normal: 40-230mg/dL) and IgE;<1 UI/ml (normal: <100 UI/ml).Flow cytometry was performed in order to determine lymphocyte subsets.Decreased total and percent B lymphocytes (40 cells/mL and 2%; normal, 100 to 400 cells/mL and 5% to 23%, respectively). Although percentages of $CD3^+$ (79%; normal: 62.8-85.0%) and $CD4^+$ T cells(28.5%; normal: 34.0-63.8%) were low, the percentage of$CD8^+$ T cells (46%) was within the normal range (normal:19-48%). As a result, a reduced CD4/CD8 ratio of 0.62was found (normal: 1.5-2.9).The levels of naïve/memory subsets (CD45RA, CD45RO) and recent thymic emigrants (CD45RA+CD31+) within the CD4+ T lymphocyte population were normalbutshowed a decreased percentage of CD8+ naïve Tlymphocyte (CD45RA+, CCR7+): 15% (normal: 42-73%).

The association of hypogammaglobulinemia, profound decrease in circulating B cells infectionand suspicion of thymoma strongly suggested Good's syndrome.Despite to all lifesaving treatments orientation, cooperation and hemodynamics got worse and the patient died of respiratory and cardiac arrest due to pulmonary embolism.

3. Discussion:

Good's syndrome, reported for the first time in 1954 by Robert Good [5,6].There are no clear diagnostic criteria for GS, but it is a distinct entity described by WHO/IUIS as a primary immunodeficiency with thymoma and hypogammaglobulinemia similar to common variable immunodeficiency (CVID) [7]. Western literature reports the incidence of GS as 5% to 10% of all thymomas, whereas it is rare in the eastern part of the globe, 0.2% – 0.3% as per Japanese literature [7].

Unlike the majority of immunodeficiencies, this disorder occurs in the 4th or 5th decade of life with an equal sex distribution [2,3]. According the literature data, the mean age of initial symptoms was56 years (range, 29–75 years) [4]. Our second case has an importance related to his age. He was 23-year-old when diagnosed as GS. This is an early age to have GS when compared to other GS cases in the literature [8,9,10,11]. The illness is hallmarked by adult-onset immunodeficiency in the setting of thymoma. Abnormal humoral immunity is a constant finding, often associated with T cells lymphopenia and/or functional impairment [3]. These findings distinguish GS from CVID and lymphoma in which lymphocytes are in normal or higher values.

Ourtwo patients featured almost all Good's syndrome "classic" manifestations, thymoma with hypogammaglobulinemia and a subsequent immunodeficiency: upper and lower respiratory tract infections, diarrhea and opportunistic infections (mucocutaneous candidiasis). Also found in the first patient,vertebral bodies hemangiomas. This association has never been reported in the literature. Although up to 31.8% of patients with GS can have diarrhea, the cause of diarrhea is still not clear. Many factors may be related to the cause of diarrhea, such as infections and malabsorption [12].Infections may be inaugural, they are related to the immune deficiency. This was the case in our two patients, where pulmonary infections were the leading reason for consultation. While most reported patients had encapsulated bacteria infections [4], our first patient experienced, besides these infections, a Pseudomonas aeruginosa infection. GS features, also, opportunistic infections (CMV, mucocutaneous candidiasis, and pulmonary pneumocystosis) [4]; only mucocutaneous candidiasis was found in the first case. Tuberculosis cases were reported in some patients with GS, in countries where the epidemiological situation is similar to that of Algeria [13]. HCV, HBV and HIV serologies were negative, however these results should be interpreted carefully as hypogammaglobulinemia could be a source of false negatives. In these cases, PCR techniques are of better diagnostic contribution. Autoimmune diseases such as myasthenia gravis, pure red-cell aplasia, pernicious anemia, diabetes mellitus, and idiopathic thrombocytopenia also occur [3]. but our patients did not have any autoimmuneconditions.

As for the immunological abnormalities found in thesepatients, hypogammaglobulinemia and partial or total depletion of B cells are consistent findings,noted in 87% of cases and the absence of pre-B cells has been reported in bone marrow samples from patients with GS [14,15].T CD4+ lymphopenia, reversed CD4/ CD8 ratio and impaired T cell response to mitogens are seen in large numbers of patients with GS. Thus, unlike X-linked agammaglobulinemia and CVID, opportunistic infections related to impaired cellular immunity are often observed which explains the poorer prognosis.The percentage of mature naïveCD8+CD45RA+CCR7+ T cells was reduced in the peripheral blood of the secondpatient. These results suggested that the spectrum of thymopoieticincompetence in thymomas may extend not only to theCD4, because of CD4+ T lymphopenia, but also to the CD8 lineage [16]. The authors raised the hypothesis that the thymus is an endocrine organ, producing factors such as a leukemia-inhibitory factor and oncostatinM that may play roles in modulating peripheral blood T celllevels [17].

The immunodeficiency occurs before, after or simultaneously with thymoma [4,18]. In our patients, the abnormalities chronology is unknown. A total depletion of B cells together with T CD4 lymphopenia were noted, ultimately resulting in a susceptibility to infections.

Surgical removal of thymoma did not correct the immunodeficiency in the first patient, as the immunological abnormalities persisted after thymectomy.Our findings were consistent with what was so far reported in the literature [2,3].

In conclusion, in a patient with thymoma and recurrent opportunistic infection, Good syndrome should be considered, and the immunological parameters should be checked. Currently, there is no satisfactory treatment. Thymectomy can prevent locally invasive growth and metastasis of thymoma, but it does not reverse dysimmunity [19]. Gammaglobulin replacement was recommended to suppress infections associated with GS.

Conflict of interest declaration
The authors declare no conflict of interest
Figure 1

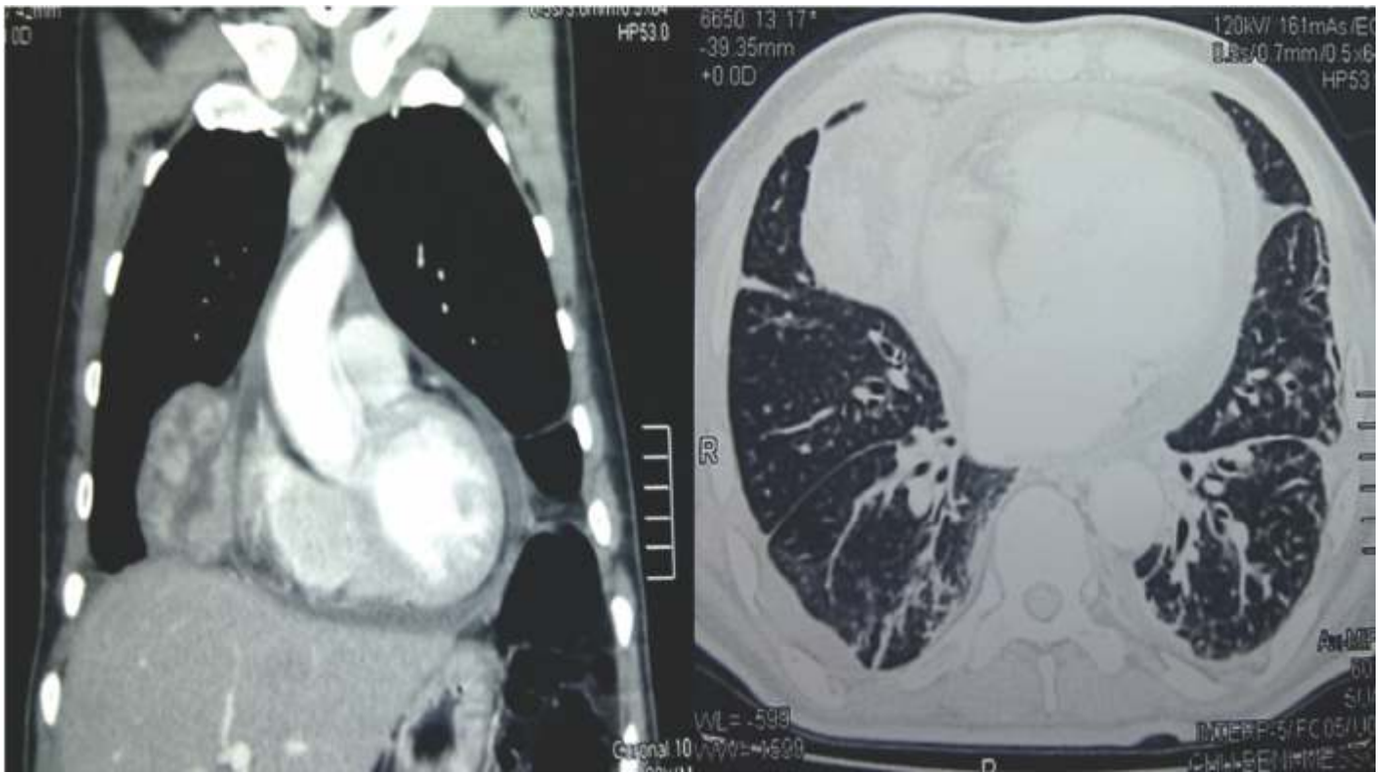

Figure 1. CT scan: on the left, mass anterolateral to heart; on the right, a thin-section CT scan showing bilateral bronchiectasis

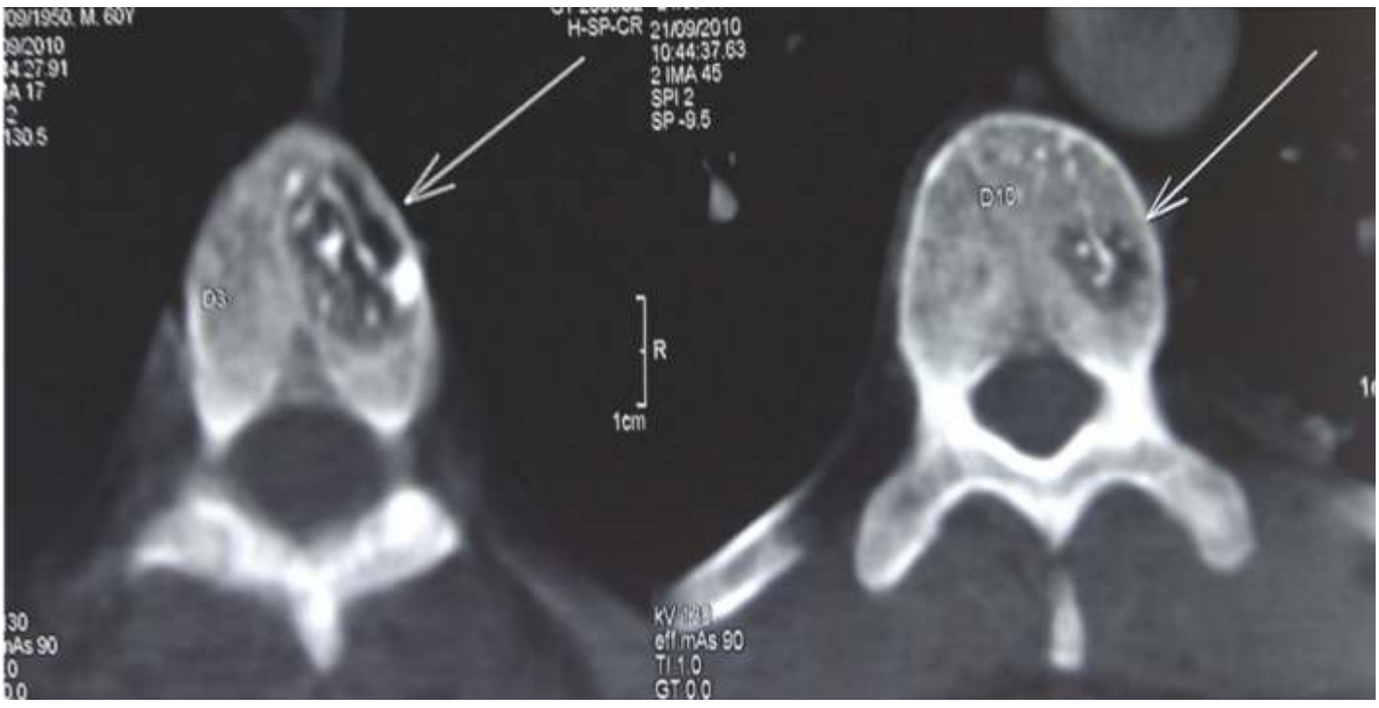

Figure 2. CT scan showing vertebral bodies hemangiomas

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