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Pulmonary Medicine

GOOD'S SYNDROME ASSOCIATED WITH CYTOMEGALOVIRUS PNEUMONIA : CASE REPORT AND LITERATURE REVIEW.

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ABSTRACT Good's syndrome is a rare entity defined by the association of a thymoma with an acquired immune deficiency characterized by hypogammaglobulinemia. We report a case of a 62 year old patient, Diagnosed and treated for thymoma. The patient presented 4 months later with severe pneumonia. Biological workup revealed hypogammaglobulinemia at the expense of all immunoglobulin classes, lymphocytopenia involving B and T CD4+ lymphocytes leading to the diagnosis of Good's syndrome. Cytomegalovirus DNA testing came back positive. The patient received immunoglobulin infusion, noting an improvement in his general condition. Good's syndrome represents 6 to 11% of para-thymic syndromes. Its pathogenesis remains unknown. Its clinical presentation is diverse, with either a mediastinal syndrome or recurrent severe infections. Cytomegalovirus is found in 40% of cases. Management is based on thymomectomy and introduction of anti-infectious agents. Hypogammaglobulinemia, rarely improved by thymomectomy, requires the addition of systemic immunoglobulins. The rarity, clinical diversity, and severity of Good's Syndrome justifies rigorous clinical and immunologic investigation when diagnosing thymoma or the occurrence of repeated severe infections, especially since therapeutic management, despite the absence of a well-defined consensus, can improve the prognosis and survival of patients.

KEYWORDS : Good's Syndrome, Hypogammaglobulinemia, Thymoma, Cytomegalovirus

INTRODUCTION

Good's syndrome is defined by the association of an acquired immunodeficiency with a thymoma. It is a rare entity that occurs in only 5 to 10% of adult thymic tumors[1] . It was first described in 1954 by Robert Good[2] . It is characterized by hypogammaglobulinemia as well as humoral and cellular immune dysfonction. In 80% of cases, hypogammaglobulinemia occurs concomitantly or within 5 years of the thymoma diganosis[3] . Patients with this syndrome are susceptible to severe and recurrent bronchopulmonary and otolaryngeal infections, sometimes leading to bronchiectasis[4] .

We report through our observation and a review of the literature, the main characteristics and clinical consequences of Good's syndrome, by underlining the importance of performing an immunological analysis with the diagnosis of thymoma, and its impact on the prognosis improvement.

Patient and Observation

A 62-year-old male patient, former smoker, was hospitalized for chronic cough with exertional dyspnea.

There was no record of recurrent infections. The initial clinical examination did not state any abnormality.

A standard chest radiograph revealed a mediastinal round opacity, occupying the upper half of the left hemithorax. On the CT scan (Figure 1 (A-B)), the mass occupied the entire anterior mediastinum, presenting close contact with the ascending aorta and pulmonary artery. There also were two left pleural nodules.

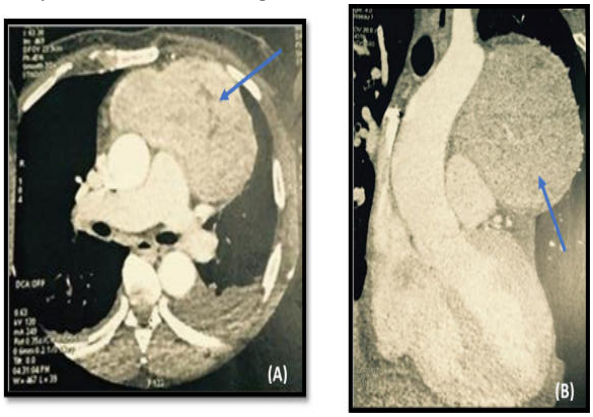

Figure 1 :
(A) Chest CT scan - cross section - showing an anterior upper mediastinal mass (blue arrow) in close contact with the ascending aorta and pulmonary trunk and arteries.
(B) Chest CT scan - coronal section - showing an anterior upper mediastinal mass (blue arrow) in close contact with the ascending aorta without tumoral invasion or compression.

A CT-guided needle biopsy was performed on the tumor and the anatomopathological analysis of the fragments confirmed the diagnosis of type B2 thymoma.

The patient underwent a preoperative workup, which stated no respiratory or cardiovascular comorbidities. The blood cell count performed prior to surgery was normal. The patient had no clinical signs of myasthenia.

Complete resection of the thymoma was performed by sternotomy, with removal of the pleural nodes. No post-operative complication was noted and the control X-ray was satisfactory. Anatomopathological study confirmed a B2 thymoma, Masaoka stage IV, due to the presence of thymic cells within the resected pleural nodules.

The patient received postoperative radiotherapy and clinical improvement was noted.

Four months later, the patient is admitted to ICU presenting with respiratory distress, fever, sputum and general condition. Clinical examination revealed diffuse bilateral crackles. There were no signs of heart failure.

Chest radiograph showed diffuse asymmetrical alveolar opacities on both lungs with predominance in the right lung (Figure 3). The patient had high C-reactive protein to 285mg/l, and negative procalcitonin. Moreover, Cytomegalovirus Polymerase chain reaction test on sputum came back positive.

In search of an immune deficiency, we performed a serum protein electrophoresis, and weight immunoglobulin dosage, which showed hypogammaglobulinemia at the expense of all immunoglobulin subclasses (Table 1).

Table 1 : Values of the Immunoglobulin Count in the Patient Serum

Subclass of immunoglobulin	Value (g/l)	Normal values
A Immunoglobulin	0,138	0,845-4,990
G Immunoglobulin	2,184	6,103-16,160
M Immunoglobulin	<0,097	0,330-2,930

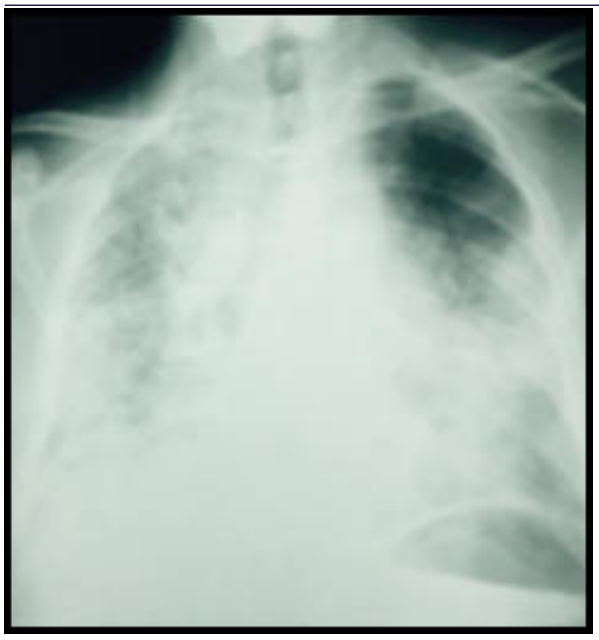

Figure 3 : Chest Radiograph Showing Diffuse Bilateral Pneumonia Predominant in the Right Lung

Lymphocyte phenotyping showed profound lymphocytopenia at 419 elements per mm^3, no circulating B cells, and decreased CD4 and CD8 T cell and Natural Killer cell counts. There was a reversal of the CD4/CD8 ratio, which was low to 0.27. All these findings endorsed us to diagnose the patient with Good's Syndrome.

The patient received five courses of intravenous immunoglobulins and was put on Co-trimoxazole. His general and respiratory state improved in days, with radiological sweep on control radiographs.

DISCUSSION

Thymomas are mediastinal tumors that have the highest percentage of association with paraneoplastic syndromes[5] .

The most common para-thymic syndrome is myasthenia (30-45%), followed by Good's syndrome (6-11%) and erythroblastopenia (2-5%), along with less common clinical manifestations[6,7].

Good's syndrome was first described more than 50 years ago. It has several definitions depending on the authors[8]. Although there are no established diagnostic criteria for this syndrome, it is considered as a distinct entity by the expert committee of the WHO and the International Union of Societies for Immunology[8]. It is defined by the association in adults of a thymoma, and acquired immunodeficiency characterized by hypogammaglobulinemia[7]. that affects all immunoglobulin classes. A more selective classification adds to the definition the presence of a reduced circulating B cell count, impaired cell-mediated immunity, and an inversion of the CD4/CD8 ratio[7,10] .

The pathogenesis of this syndrome remains uncertain. It is suggested that the origin of the deficiency is the bone marrow[11]. To date, three hypotheses have been put forward to explain this phenomenon: the first is that there is an abnormality in cytokines produced by the stromal cells of the bone marrow, which influence the growth and differentiation of B precursors[12]. Then comes the possibility of a deficit in memory CD4+ T cells, given the susceptibility of patients with Good's syndrome to opportunistic infections[11]. It is also possible that T cells and autoantibodies produced directly or indirectly inhibit the functions of B cells, by immunological phenomenon[13]. It has been shown that CD8+ T cells are able to repress the proliferation of B progenitors, the main immunological consequences of which are the absence of B cells in the blood and hypogammaglobulinemia[14] .

The diagnosis of Good's syndrome may precede, accompany, or follow that of thymoma. In a systematic review including 188 studies, Kelesidis and Yang[7] found that the diagnosis of thymoma preceded that of hypogammaglobulinemia in 42.4% of cases.

The delay for our patient, between the discovery of the thymoma and the infectious symptomatology that revealed the hypogammaglobulinemia was four months.

Usually diagnosed during the 5th or 6th decade, without gender predominance[4,14] , the mean age of onset is 56-59 years, and the mean age of diagnosis of both entities (thymoma and hypogammaglobulinemia) is 62 years[7,15,16,17], which correlates with our case. Good's syndrome is extremely rare in children[18].

The circumstances of discovery of Good's syndrome are various, generally related to the preceding entity. It may be, as in our patient's case, clinical manifestations related to the tumor associating cough, chest pain, dyspnea and/or superior vena cava syndrome. An anterior mediastinal mass may be discovered incidentally on a chest radiography. The diagnosis of Good's syndrome should also be considered in the presence of recurrent infections . Patients presenting with this syndrome have increased susceptibility to bacterial, fungal and viral infections due to immune deficiency. The most frequent are recurrent rhinosinusitis and bronchopulmonary infections, which often cause bronchiectasis[15,17].

Haemophilus Influenzae and Pseudomonas spp are the most frequently identified pathogens. Only 2 cases of Mycobacterium tuberculosis have been reported in the literature[7,13] and more recently, cases of COVID-19 infection have been described [19] .Opportunistic fungal and viral infections are due to cell-mediated immune deficiency and involve several opportunistic germs, mainly Cytomegalovirus, found in 40% of cases, Candida, but also Herpes Simplex, Herpes Zoster, Aspergillus, Pneumocystis jirovecii[7,9,13] .

In the literature review reported by Kelisidis et al, 90% of thymomas associated with Good's syndrome are benign, and mostly type AB (41.7%); Type B2 is reported in 25% [7].

The correlation between thymoma and hypogammaglobulinemia in Good's syndrome is not well established. IgG, IgA and IgM are the immunoglobulins that play a role in anti-infectious immunity. As seen in our patient's results, all immunoglobulin subclasses are predominantly deficient[7,17] .

Management of thymoma is based on complete surgical resection, which remains an important prognostic factor for survival[20]. In advanced stages, radio-chemotherapy is often required[7,9]. Thymectomy prevents the dissemination of tumor cells and often allows the regression of certain parathymic conditions including myasthenia and erythroblastopenia[21]. However, its benefit on hypogammaglobulinemia and recurrent infections has not yet been established[9,22,23]. Hypogammaglobulinemia usually persists despite thymectomy which supports the theory that autoantibodies and other immunological mechanisms are involved in the pathogenesis of Good's syndrome[22] .

Infectious complications are the major factor affecting the long-term prognosis in Good's syndrome. With an overall mortality rate of 46%, the part of infectious causes is 60%[7] . The depth of B-cell deficiency and hypogammaglobulinemia, and the degree of impaired cell-mediated immunity, are the major determinants of infections' severity[7,24]. Thus, intravenous immunoglobulin therapy is the mainstay of Good's syndrome management, as it has been shown that administration of gammaglobulin not only decreases the frequency of sinus and bronchopulmonary infections, but also provides better control of infection when it does occur, with less use of antibiotic therapy and shorter average hospital stay[13,17].

Although infection is the main cause of morbidity and mortality in Good's syndrome, there is considerable evidence that hematological complications and the association with other autoimmune manifestations may worsen the prognosis[24,25] .

CONCLUSION

Good's syndrome is an uncommon entity, but its severity requires careful clinical, biological and immunological investigation. Its clinical presentation is variable, and infectious complications may precede, accompany or follow the appearance of thymoma, which justifies the performance of an immune assessment in the presence of any anterior mediastinal mass in adult patients, or in case of recurrent bronchopulmonary infections with or without bronchial dilatations. Because of the interval between the occurrence of the immune

deficiency and the discovery of the thymoma, immune testing should be repeated in the slightest doubt. Although there is still no clear protocol for therapeutic management, it is currently recognized that regular administration of intravenous immunoglobulins improves the prognosis of Good's syndrome by reducing the incidence of infections. This is where the value of early diagnosis lies. It is also crucial to detect the various parathymic syndromes that are often associated with Good's syndrome, the presence of which would require adjustment of the patient's management.

Abbreviations :

DNA : Deoxyribonuclease Acid
CT : Computed tomography
ICU : intensive care unit

Consent

An informed consent was obtained from the patient for the publication of this case report and any accompanying images

Disclosure

This case report was written based on clinical observation without any funding.

Conflicts of Interest

There are no conflicts of interest between the authors and the patient.

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