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*LETTER TO THE EDITOR*

# IS HYPOGAMMAGLOBULINEMIA A CONSTANT FEATURE IN GOOD'S SYNDROME?

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**Thymomas are rare tumors, which can be associated to a variety of paraneoplastic syndromes, including a fatal hypogammaglobulinemia, namely Good's Syndrome (GS). Although the combination of thymoma and hypogammaglobulinemia is regarded as sufficient for diagnosis of Good's syndrome, some thymoma patients with a clear clinical picture of immunodeficiency present normal levels of immunoglobulins. We describe the case of a patient, with a 20-year history of thymoma, who underwent several operations and lines of chemotherapy, and suffered from recurrent infections, including one rare skin infection from *Pseudoallescheria boydii*. The patient constantly presented normal levels of gammaglobulins.**

Good's syndrome is named after Dr Robert Good, who described a case of hypogammaglobulinaemia in an adult affected by thymoma in 1956 (1). Although formal diagnostic criteria are yet to be definitely established for this disorder, Good's syndrome is classified as a distinct entity by the expert committee of the World Health Organisation/International Union of Immunological Societies on primary immunodeficiencies as one of the "Predominantly antibody deficiencies" (2). In patients with thymoma, the incidence of hypogammaglobulinaemia is 6–11%. The syndrome is characterized by the presence of immunodeficiency that may present before or after the diagnosis of a thymoma, usually in the 4th or 5th decade of life. The clinical picture is similar to that seen in patients with X linked agammaglobulinaemia (XLA) and common variable immune deficiency (CVID). Sinopulmonary infections are the most commonly reported, followed by bacterial urinary tract and skin infections. In contrast to XLA and CVID, opportunistic infections associated with disorders of cell mediated immunity commonly occur in Good's syndrome, particularly cytomegalovirus (CMV) colitis and retinitis and mucocutaneous candida infection, even if opportunistic infection caused by herpes simplex, human herpesvirus 8, varicella zoster, and *Pneumocystis carinii* pneumonia have also been described. Nearly 50% of patients suffer from diarrhea, mostly aspecific, although in several occasion enteric bacteria, giardia, and CMV have been isolated (3-4).

The question of proper criteria for diagnosis of Good's syndrome continues to represent an unresolved question. In a recently published systematic review (4), presence of thymoma and hypogammaglobulinaemia were chosen as minimum criteria for diagnosis. Such an approach is effective and easily applicable both in clinical practice and scientific research, but it presents the risk of missing

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immunodeficiency syndromes in thymoma, which might present with an impaired B cell function, but not low immunoglobulin levels. The case we present here focuses on this important aspect, as our patient presented several features typical of Good's syndrome, except for hypogammaglobulinemia.

*Case history*

The patient, a male Caucasian, presented with a twenty-year history of thymic carcinoma associated to myasthenia gravis. In 1989, at the age of 33 year, he underwent radical thymectomy with adjuvant chest radiotherapy (surgical stage IIB according to Masaoka Staging System, grading B2 according to WHO criteria), and remained disease-free until 1998, when a recurrent lesion was firstly detected in the right lung and successfully managed by the surgeon. The patient also underwent additional operations in 1999 and then in 2006 for surgical removal of relapsing tumors in the right pulmonary inferior lobe and in the right pleural paravertebral region. Interestingly, at histology analysis, all recurring lesions showed a less differentiated pattern of thymic carcinoma (grading B3 according to WHO criteria) with respect to the original tumor. He also developed painful bone metastasis to the vertebral column with compression of the spinal cord, for which he received palliative radiotherapy and monthly zoledronic acid. As shown in Table I, from 2000 until recently, the patient received monthly injections of somatostatin analogs (positive Octreoscan scintigraphy), and several lines of systemic chemotherapy in order to treat lesions localized in the diaphragm, lung, pleura and mediastinum with transient responses and variable periods of disease stabilization, documented by TAC and bone scans. As detailed in Table I, he underwent various polychemotherapy regimens, including platinum-doxorubicin-cyclophosphamide, oxaliplatin-etoposide, gemcitabine-capecitabine, cisplatin-ifosfamide-vinblastine, and single-agent chemotherapy regimens based on oxaliplatin and lyposomial doxorubicin. He was also administered targeted agents such as cetuximab, imatinib and sorafenib. No particular or unexpected side effect was reported associated with the treatment. In 2008, the patient suffered from pulmonary embolism associated to deep venous thrombosis, during a course of capecitabine-gemcitabine, but this episode was considered to be unrelated to cytotoxic therapy. Of note, the patient obtained a prolonged disease stabilization from December, 2004 to September, 2005, with administration of 32 consecutive cycles of weekly cetuximab, with no relevant treatment-related side effect except for typical grade 1-2 malar rash.

Although immunodeficiency was not present at first diagnosis, from 2004 the patient referred with increasing frequency recurrent respiratory *infections*, which were empirically treated with various antibiotics (mostly penicillins, cephalosporins and fluoroquinolones) and mucolytic agents, and chronic diarrhea, which was managed with antibiotics and symptomatic medications. In May 2005, B cell count and immunoglobulin blood levels were assessed for the first time. As depicted in Table II, the patient presented almost no circulating B cells, while immunoglobulin levels were within the normal ranges (IgG: 560 to 1800 mg/dL, IgM: 45 to 250 mg/dL, IgA: 100 to 400 mg/dL). On suspicion of Good's disease, we postulated that hypoimmunoglobulinemia could be cyclic and therefore we regularly checked both immunoglobulin and B cell levels. Surprisingly, as shown in Table II, this picture appeared unmodified in the course of time. Another peculiar finding was that IgG titles against common pathogens such as CMV, EBV and HSV-1 and -2 were very high, about 10-100 times the minimum dilution ratio necessary for positivity. Also, as generally occurs in Good's syndrome, the CD4+/CD8+ ratio was constantly inverted.

In January 2009, the patient developed a cutaneous infection in the lower right limb. which clinically evolved from erythematous to pustulous and then ulcerous and crosteous lesions. Antibiotics (penicillins, cephalosporins and vancomicine) were ineffective. Excisional biopsy of an ulcerous lesion showed inflammation and necrotizing granulomas, which appeared to be consistent with a diagnosis of atypical mycobacteriosis. Nevertheless, cultures were repeatedly negative until April, 2010, when the fungus *Pseudoallescheria boydii* was isolated. From November 2009, the patient also suffered from chronic inguinal abscess (*S. aureus* and *E. Coli* were isolated) for which he received antibiotics. Despite normal immunoglobulin levels in the blood, at this point the clinical picture induced us to

**Table I.** *Chemotherapy regimens administered.*

| | | | |
|---|---|---|---|
| OXALIPLATIN | 70 mg/mq | Day 1,8 every 28 days | 4 cycles |
| CETUXIMAB<br>+<br>OXALIPLATIN + LYPOSOMIAL DOXORUBICIN | 250 ng/mq<br>+<br>70 mg/mq + 20 mg/mq | Weekly,<br><br>Every 21 weeks | 37 weeks<br>+<br>14 cycles |
| GEMCITABINE –<br>CAPECITABINE | 800 mg/mq -<br>850 mg/mq bid | Day 1,8 –<br>Days 1-14 | 1 cycle |
| GLEEVEC | 400 mg | daily | 2 cycles |

administer standard human immunoglobulins, which appeared to cause no improvement to the patient's clinical conditions. After cultural diagnosis, the mycotic infection in the leg seemed to improve on voriconazole, but in May, 2010 the patient developed a *Pseudomonas aeruginosa* pneumonia and died shortly afterwards.

## DISCUSSION

We reported this case because of its several particularities, which we believe deserve commenting and discussion. Our patient presents a history of immunodeficiency related to thymoma with several features typical of Good's syndrome, such as low B cell count and a CD4+/CD8+ inverted ratio. We previously reported on some thymoma immunodeficient patients presenting with low B cell count and normal immunoglobulin levels (5-6) and defined this condition TID (thymoma-associated immunodeficiency). The question is: should we really consider TID as a separate clinical entity or should it be identified with Good's syndrome, on the grounds of low B cell count, the CD4+/CD8+ inverted ratio and clinical presentation? It is true that in a recent systematic review of Good's syndrome, 100% of patients with Good's syndrome did present with low immunoglobulin levels, but this simply reflects the adopted definition of Good's syndrome, identified with thymoma plus hypogammaglobulinemia. The key concept that needs to be discussed here is that simple measurement of immunoglobulin levels gives no information about their actual activity and that therefore an immunoglobulin deregulation might not be detected. Unfortunately, the present case was not studied in order to detect the patient's capacity to mount an antibody response. High blood levels of antibodies directed against common viruses makes it possible to speculate that the activity of memory B cells, not present in the blood, may be preserved and responsible for normal immunoglobulin levels and absence of opportunist

**Table II.** *Immunoglobulin and B-cell (CD19) levels and CD4/CD8 ratio of the patient.*

| | Ig G | IgM | IgA | CD19 % | CD4/CD8 ratio |
|---|---|---|---|---|---|
| May 2005 | 592 | 88 | 134 | 1 | 0.2 |
| Dec. 2005 | 755 | 76 | 143 | 2 | 0.3 |
| Jul. 2006 | 853 | 63 | 159 | 6 | 0.45 |
| Oct. 2007 | 868 | 50 | 152 | 7 | 0.4 |
| Feb. 2008 | 686 | 45 | 138 | 3 | 0.2 |
| Sept. 2008 | 844 | 39 | 120 | 3 | 0.35 |
| Mar. 2009 | 740 | 78 | 119 | 1 | 0.4 |
| Jun. 2009 | 892 | 80 | 158 | 0.8 | 0.2 |
| Sept. 2009 | 739 | 47 | 161 | 0.9 | 0.3 |
| Dec. 2009 | 823 | 56 | 147 | 1 | 0.35 |
| Feb. 2010 | 898 | 81 | 149 | 2 | 0.2 |

infections like CMV or HSV in our patient. On the other hand, the capacity to develop an antibody response to new antigens might be impaired and be responsible for the immunodeficiency syndrome along with deregulation of other components of the immune system. Normal immunoglobulin levels in the blood induced us to not administer standard i.v. immunoglobulins until the very late stages of the disease, with no apparent positive clinical effect. As the patient's immunoglobulins could have been non-functioning, it is possible to hypothesize that earlier immunoglobulin administration might have been beneficial for him.

Another interesting aspect of this case is the very rare infection that affected our patient. To our knowledge, ours is the first reported case of *Pseudoallescheria boydii* infection in a patient with Good's syndrome. Due to the rarity of this fungus, cultural diagnosis was delayed and a proper therapy could not be established until shortly before patient's death. On the basis of a very similar report in an immunocompromised patient, retrieved from literature (7), the patient was treated with voriconazole, although the late diagnosis prevented the treatment from being fully effective.

Finally, it is noteworthy that our patient obtained long-lasting disease stabilization with cetuximab. We have previously reported partial responses in

two advanced, chemorefractory thymic carcinomas, with strong expression of the Epidermal growth factor receptor (EGFR) on immunohistochemistry (8). In the case presented here, cetuximab was indeed very well tolerated and managed to delay disease progression for about 8 months. This case adds to the existing growing body of literature (8-9) and encourages further research in this direction. At the present time, a phase II trial is undergoing evaluating neoadjuvant cetuximab plus chemotherapy in inoperable thymic tumors, with a target accrual of 28 patients and primary end-point set to be the rate of complete responses to treatment (10).

This case was presented with the intent to draw scientific interest to a particular population of thymoma patients, presenting an immunodeficiency syndrome closely resembling Good's syndrome, except for normal immunoglobulin levels. Our opinion is that this kind of patient could be diagnosed with Good's syndrome. The need for a better definition of Good's syndrome, which does not simply rely on immunoglobulin levels, but on other more reliable parameters evaluating actual functioning of the B cell component and antibody response, is compelling, as an unknown proportion of Good's patients might miss diagnosis. The rarity of infection our patient presented and the long-lasting stabilization obtained with cetuximab are also interesting matters of discussion and worthy of reporting.

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