Clinical Case Report

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Occasional detection of thymic epithelial tumor 4 years after diagnosis of adult onset Still disease

A challenging case report and immuno-oncological considerations coming from pertinent literature review

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Abstract

Background: Thymoma is a T cell neoplasm arising from the thymic epithelium that due to its immunological role, frequently undercover derangements of immunity such a tumors and autoimmune diseases.

Methods: Herein, we report, to the best of our knowledge, the first description of an association between thymoma and adult onset Still disease (AOSD) in a 47-year-old man. The first one was occasionally detected 4 years later the diagnosis of AOSD, and surgically removed via right lateral thoracotomy. Histology confirmed an encapsulated thymic tumor (type AB sec. WHO-classification).

Results: The AOSD was particularly resistant to the therapy, requiring a combination of immunosuppressant followed by anti-IL1R, that was the only steroids-sparing treatment capable to induce and maintain the remission. The differential diagnosis was particularly challenging because of the severe myasthenic-like symptoms that, with normal laboratory tests, were initially misinterpreted as fibromyalgia. The pathogenic link of this association could be a thymus escape of autoreactive T lymphocytes causing autoimmunity.

Conclusion: Clinicians should be always include the possibility of a thymoma in the differential diagnosis of an unusual new onset of weakness and normal laboratories data, in particular once autoimmune disease is present in the medical history.

Abbreviations: AOSD = adult onset Still disease, CRP = C-reactive protein, CT/PET = computed tomography/Positron emission tomography, FDG = fluoro-2-deoxy-D-glucose, MG = myasthenia gravis, SUV = standard uptake value.

Keywords: adult onset Still disease, autoimmune disorders, thymic epithelial tumors, thymoma

1. Introduction

Adult onset Still disease (AOSD) is a rare autoinflammatory condition,[1–3] initially described by Bywaters in 1971.[4] Nowadays, it is defined by a panel of clinical and laboratory criteria of whom the most widely accepted are those of Yamaguchi.[5] These include 4 major and 4 minor criteria. Diagnosis is made when there are 5 or more criteria which include at least 2 major criteria. In current clinical practice, daily fever and arthromyalgias are almost mandatory and in vast majority of the patients these symptoms are accompanied by elevated acute phase reactants, included hyperferritinemia (>5000 μg/L) on absence of specific markers of disease. Other symptoms, like lymphadenopathy, splenomegaly, sore throat, pleuritis, pneumonitis, or pericarditis, are also frequently reported.[6,7]

Aspecific symptoms and signs of AOSD require the exclusion of infections and neoplasm since a paraneoplastic AOSD-like syndrome in the course of solid tumor, and hematopoietic malignancy have been reported. However, other case reports suggest the presence of a true AOSD mostly preceding malignancy of an average of 9 months. It is controversial whether the presence of AOSD could be coincidental or in some way related to the subsequent neoplasm onset.[8]

Herein, we report a challenging case of a 47-year-old man who developed a thymic epithelial tumor (thymoma AB sec. WHO-Classification[9]), 4 years after the initial diagnosis of AOSD.

We may speculate on the fact that the underlying thymoma probably represents the true trigger of the preceding AOSD; indeed, it is well known that besides myasthenia gravis (MG), other autoimmune disorders may occur in thymoma patients and that over two-thirds of these autoimmune disorders occurred before thymoma resection.

Among these autoimmune disorders a co-occurrence between thymoma and AOSD has never reported since now in the literature, to our best knowledge.

2. Case report

In September 2010, a 46-year-old man was admitted in medicine department for arthromyalgias, remitting fever up to 39°C,

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Written informed consent was obtained from the patient for publication of this Case Report and any and all accompanying images.

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accompanied by shivering and confluent erythematous macules and papules on the trunk; all the symptoms gradually onset 1 month before. Laboratory profile revealed neutrophilic leukocytosis 15,000 nL (nv 2000–8000 nL), Hb 10.5 mg/dL, C-reactive protein (CRP) 15.66 mg/dL (nv 0.05–0.30), erythrocyte sedimentation rate (ESR) 123 mm/h (nv < 30 mm/h), and ferritin 5381 ng/mL (nv 25–350 ng/mL). The following tests resulted negative: procalcitonin, repeated blood and urine cultures, antibodies to parvovirus B19, toxoplasma, rubivirus, cytomegalovirus, herpes viruses type 1 and 2, rickettsia, Widal–Wright reaction, rheumatoid factor, Waaler–Rose, C3, C4, chest X-ray, and ultrasound evaluation of the abdomen.

The start of corticosteroid treatment (oral prednisone at the dose of 25 mg t.i.d.) resulted in a gradual subside of the symptoms; 1 month later, in the subsequent rheumatological control, CRP was 0.07 mg/dL, ferritin 487 ng/mL, and ESR 20 mm/h. Methotrexate 10 mg/wk was shortly added as a steroid sparing agent. In December 2011, at the dose of 25 mg/d of prednisone, the patient got worst with increasing artrhalgias and subjective poor conditions, although CRP and ESR levels were in the normal ranges. In this occasion, leflunomide 20 mg/d was added to methotrexate and prednisone. Physical well-being was obtained only maintaining prednisone over 17.5 mg/d. Hence, in April (7 months after the initial diagnosis), the Anakinra 100 mg/d (anti-IL1R) replaced MTX and LF; at this moment a further chest X-ray did not revealed any radiological abnormalities; moreover, laboratory tests were normal: CRP: 0.6 mg/dL (nv 0.05–0.30) and ESR: 40 mm/h (nv < 30).

In September 2012, despite an unremarkable laboratory profile, the patient complained muscle ache and weakness on his legs. A complex diagnostic work-up examination was started but all the examinations and visits (transthoracic echocardiogram, magnetic resonance imaging of lumbar spine, magnetic motor evoked potentials, neurosurgical and cardiological examinations) did not found any pathological signs. On April 2013, neurological assessment was within the limits but due to the subjective weakness after a sustained walk and the episodic lowering of the speech, we investigated the presence of antiacetilcholin receptors with a negative result. In November 2013, the patient's complains were hence dismissed as severe fibromyalgia and treated with selective serotonin receptor inhibitors and gabapentin.

About 1 year later (October 2014), a chest computed tomography (CT) scan was performed as part of the radiological surveillance of an antibiotic-resistant pneumonia. A paracardiac solid mass was identified (Fig. 1A and B) and a CT/Positron emission tomography (PET) scan showed that the mass had a mild ^{18}F- fluoro-2-deoxy-D-glucose (FDG) uptake (standard uptake value [SUV]-max 3.4, Fig. 1C) without specific suggestions about its nature. The lesion was surgically removed via right lateral thoracotomy and definitive histology was indicative of an encapsulated thymic tumor (type AB sec. WHO-classification, Fig. 1D). No adjuvant therapies were recommended according with histology and staging of disease (no capsular invasion). In January 2016, the patient reported to be in good condition, the myalgias and weakness were subsided and he is still on Anakinra treatment to maintain the remission of AOSD.

3. Discussion

Thymomas are rare neoplasms with an overall incidence in the United States of 0.15 cases per 100,000 person-year.[10] From a histological point of view, most thymomas are composed of a

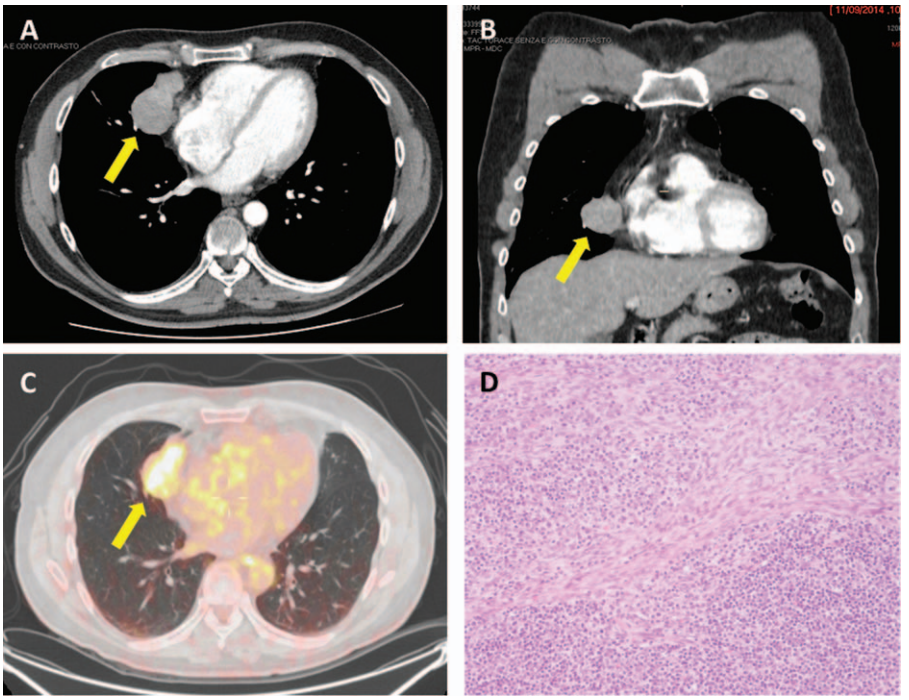

Figure 1. Radiologic evaluation (A and B): the chest CT-scan showed a lobulated para-cardiac mediastinal mass measuring 51 mm of maximum diameter; 18F FDG PET/CT scan (C) revealed a mild uptake of the radiotracer (SUVmax: 3.2) at this level; pathological evaluation (D) showed the presence of an epithelial encapsulated thymic tumor (type AB). CT = computed tomography, FDG = fluoro-2-deoxy-D-glucose, PET = Positron emission tomography, SUV = standard uptake value.

mixture of neoplastic epithelial cells and non-neoplastic lymphocytes, with the proportion among them varying widely from case to case.[11] There is a certain body of evidence demonstrating that the thymus plays a central role in the immune system, because it is the site of maturation for T cells.[12] Indeed, the thymus' primary functional role concerning the immunological system is to process the T-lymphocyte selection and maturation (the so-called "negative selection process"). In a normal working condition, only self-tolerant and immune-surveillant (against antineoplastic cells) T-lymphocytes are released systematically from the thymus.[13] Therefore, considering the role of immune-surveillance played by the thymic gland, it emerges why thymic neoplasms are associated with immunodeficiency and autoimmune disorders. In detail, among human neoplasms, thymomas are associated with the highest frequency with paraneoplastic autoimmune disorders.[11]

Even excluding MG (the most common autoimmune disease associated with thymomas), a wide variety of other autoimmune conditions are associated with epithelial thymic tumors, of which the most common are hematological (aplastic anemia, pure red cell aplasia, and Good syndrome), neurological (plymyositis, neuromyotonia, limbic encephalitis, and psychosis/sleep disorders), cutaneous (pemphigus, vitiligo, alopecia, and lichen), and generic ones (systemic lupus erythematosus, thyroiditis, ulcerative colitis, and glomerulonephritis).

On the other hand, AOSD is a rare autoimmune disease characterized primarily by a clinical triade (daily spiking daily fever, arthritis, and cutaneous rash). Considering the absence of a definitive diagnostic test, the diagnosis of AOSD is purely based on clinical examination, and often necessitates the arduous exclusion of potential mimickers such as infectious, autoimmune or autoinflammatory diseases and neoplasms; in particular, the exclusion of malignancy is of special concern, and all malignant diseases especially lymphomas, solid cancers, and myeloproliferative disorders should be taken into account in this sense.

We have herein reported a challenging case of a young man who presented with a thymoma 4 years after the clinical and laboratoristic diagnosis of AOSD according to the Yamaguchi criteria.[5] There is an ongoing debate about the co-occurrence of AOSD and solid cancers; it is controversial whether it is a paraneoplastic syndrome or just a coincidence. Indeed, it is not easy to distinguish them. As reported by Hofheinz et al,[14] in case a neoplastic disease is diagnosed in a patient, who had been diagnosed with AOSD, various categories of relationship are possible: a true paraneoplasia, a misinterpretation of tumor symptoms for AOSD, mere coincidence, or a monoclonal malignant proliferation of immune cells due to strong, initially polyclonal autoimmune proliferation, or during immunosuppressive therapy.

One can speculate that if the corticosteroid treatment could resolve the symptoms, the possibility of coincidence is more reasonable. However, it is not always true in the case of AOSD, considering that generally patients necessitate agents other than corticosteroids, such as anti-TNFs, interleukin-1, and 6 blockers, to resolve their symptoms. On the contrary, given the fact that paraneoplastic syndromes occur due to the effects of certain mediators, these mediators might also be involved in the development of paraneoplastic AOSD. Therefore, the achieving of a good clinical response to corticosteroids in such scenario would not be an unexpected situation.

In a recent review performed by Hofheinz et al,[14] the pertinent literature was retrospectively evaluated using the criteria of Yamaguchi,[5] Fautrel,[15] and Crispin;[16] a total of 36 patients fulfilled at least 1 of these sets of criteria and therefore are considered malignancy-associated AOSD. In 72% of all cases, AOSD-related symptoms preceded the tumor diagnosis (by a median of 9 months) whereas in few cases (8 patients), the onset of AOSD symptoms and the detection of a neoplasm occurred simultaneously. Finally only in 2 cases, they appeared after the detection of a malignancy or during its treatment.

In the present case, considering the very indolent behavior of thymoma WHO-Class AB,[17] we may speculate that the neoplasm could be occurred before or synchronously with AOSD but "missed" at physical examination at that time. In fact, very often the diagnosis of thymoma is incidental during routinary investigations performed for other reasons; indeed, such neoplasms are often not related with specific symptoms, especially in early-stage tumors. Since some malignancies could not be detected at the time of the initial diagnostic work-up examination, the present case may emphasize the possibility to consider the presence of an underlying neoplasm, not only at initial evaluation, but also during the follow-up.

Commonly encountered clinical (fever, sore throat, arthralgia, arthritis, and rash) and laboratory (leukocytosis, increased acute phase reactants, and hyperferritinemia) features of malignancy associated with AOSD were similar to primary AOSD.

Solid tumors originated from a wide variety of organs and tissue types with ductal breast cancer (n = 4) and nonsmall cell lung cancer (n = 3) being the most frequent histological entities. In 12 of all 18 patients with solid tumors, metastatic spreading was already described at the time of diagnosis.

There is no mention of epithelial thymic tumor in association with AOSD and this datum arouses, in our opinion, a certain interest. Indeed, as remarked above, among human neoplasms, thymomas are associated with the highest frequency with paraneoplastic autoimmune disorders.

Since 2009, there have been 5 case reports, which describe PET-CT as the key to diagnosis in maAOSD. In these patients, the malignant process was revealed by an increased tracer uptake.

In the present case, the 18F-FDG PET/CT showed a light uptake of the tracer at the level of the mediastinal mass, as a consequence of the very indolent behavior (and consequent low mitotic count) of this tumor. In fact there is a certain body of evidence[18,19] suggesting that thymomas A or AB presented with very low uptake values at 18F-FDG PET/CT whereas an intense uptake may be expected in more aggressive thymic tumors.

Concerning the treatment, corticosteroid therapy is usually the first therapeutic option in AOSD-patients. In our case, at the time of clinical diagnosis of AOSD, a corticosteroid therapy obtained a preliminary substantially complete remission of the clinical and laboratories' abnormalities. Later on, this positive effect fainted and the Anakinra was required to obtain a prolonged remission. Reviewing the literature, Hofheinz[14] observed that among 36 patients with malignancies associated with ASOD, a pharmacological therapy based on corticosteroids has been given to 31 patients achieving a clinical response in 19 of them (12 complete response and 7 partial response). There is no clear information regarding the clinical course of AOSD according with the treatment of the associated malignancy. In the present case, we observed a remarkable improvement of the patient's condition with the initial steroids dosage. However, the initial necessity to escalate the treatment to Methotrexate and Leflunomide, and the following switch to Anakinra, clearly supports the presence of a 2 different conditions; probably in causative association more than mere coincidence among the 2. In fact it is well known that the high prevalence of autoimmune diseases co-existing with

thymomas. Actually, to answer to the challenging question (Is a malignancy correlated with onset Still disease or is it just a coincidence?), we should accurately investigate the frequency of both entity to estimate the probability of a causal association. As correctly remarked in,[14] it is hard to get to accurately estimate the real frequency of the malignancies associated with AOSD. After a review of the clinical records coming from the 7 larger published cohorts of AOSD patients, the authors supposed a probable frequency well below 2% of ASOD associated with malignancy. In the present case, we report an association between 2 different very rare disease; overall incidence of the thymoma is estimated in United States of 0.15 cases per 100,000 person-year while the annual incidence of AOSD in Europe consists around of 0.4/100,000 adults. These data seem to support the hypothesis that causative association (thymoma related to the AOSD onset) more than mere coincidence could exist and deserve specific confirmatory analysis.

Finally, in almost all published malignancy-associated AOSD cases,[14] these occurred simultaneously with the underlying neoplasm or its relapse, and probably the same occurred in the present case supporting the hypothesis that thymoma represents a condition favoring the onset of autoimmune derangement.

4. Conclusions

Adult onset Still disease (AOSD) is a rare autoinflammatory condition, defined by a panel of clinical and laboratory criteria. Several solid and nonsolid neoplasms have been reported in association with AOSD but the relationship between the neoplasm and autoinflammatory disease has not been yet clarified. Herein we have reported a unique case of thymic neoplasm occurring 4 years after the diagnosis of AOSD. It could be reasonable to assume that the underlying thymoma probably represents the true trigger of the preceding AODS, considering that besides MG, other autoimmune disorders occur in thymoma patients, often anticipating the final diagnosis of thymoma.

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