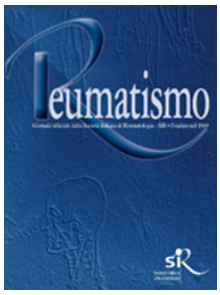

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# Development of thymoma without myasthenia gravis in a patient with radiographic axial spondyloarthritis treated with tumor necrosis factor-α inhibitors

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**Summary**
Thymic tumors are rare in the general population, and to the best of our knowledge, no cases of thymoma have been described in patients with rheumatic diseases treated with tumor necrosis factor (TNF)-α inhibitors, except the case of a patient receiving infliximab for Crohn's disease (CD) who developed a B2 thymoma.
We describe a 60-year-old Caucasian male with radiographic axial spondyloarthritis (r-axSpA) and CD who developed an AB-type thymoma without myasthenia gravis after 18 years of treatment with TNF-α inhibitors. The patient had received the same molecule since the r-axSpA/CD diagnosis and changed it 6 months before the diagnosis of thymoma due to a disease flare. At the time of the drug switch, no mediastinal mass was present on the chest X-ray. The thymoma was surgically removed, and no additional therapy was needed. Treatment with TNF-α inhibitors was reintroduced after surgery.
This case raises some important questions that remain open and deserve to be addressed in the future, such as the association between immunosuppressive therapy and thymoma and the controversial relationship between TNF-α inhibitors and myasthenia gravis.

## Introduction

Thymic tumors are a rare, albeit heterogeneous, group of malignancies with a broad range of clinical presentations. Thymoma is the most frequent subtype, with an estimated incidence of 0.13-0.32/100,000/year and accounting for 0.2-1.5% of all malignancies (1). Thymomas are associated with autoimmune diseases more often than other malignancies. Herein, we report the case of a patient with radiographic axial spondyloarthritis (r-axSpA) and Crohn's disease (CD) developing thymoma without myasthenia gravis following treatment with biologic disease-modifying anti-rheumatic drugs.

## Case Report

We describe the case of a 60-year-old Caucasian man with r-axSpA and CD, both diagnosed in 2004, arterial hypertension, dyslipidemia, and cluster headache. He had been successfully treated with adalimumab since r-axSpA/CD diagnosis, but in April 2022, a peripheral disease flare occurred and adalimumab was withdrawn [Disease Activity Score (DAS) 44 = 3.22; Ankylosing Spondylitis Disease Activity Score (ASDAS) = 2.7]. Screening exams for hepatitis B and C viruses, and tuberculosis (also including a chest X-ray) were performed, and all results were normal; therefore golimumab 50 mg monthly was started. Within 3 months, remission was achieved (DAS44=1.6, ASDAS=1.3). In December 2022, an episode of dyspnea and chest pain occurred and the patient performed another chest X-ray which showed the presence of a mediastinal mass, confirmed by chest computed tomography scan (Figure 1). The radiologist reported the mass being in close continuity with the anterolateral profile of the ascending aorta, as well as with the right atrium and superior vena cava. The patient had neither symptoms nor clinical/serological abnormalities suggesting a concomitant autoimmune disease. Good's syndrome was also ruled out since circulating gamma globulins were normal. The mass was surgically removed, and its histological assessment was consistent with a type AB thymoma (1). Post-surgical oncology consultation did not deem appropriate further treatments, such as chemotherapy or radiotherapy, and recommended restarting golimumab to prevent AS/CD flares.

## Discussion

Long-term safety data on biologic disease-modifying anti-rheumatic drugs and cancer have accrued, showing a comparable or minimally increased risk in patients with rheumatic diseases receiving these drugs (2, 3). To the best of our knowledge, no cases of thymoma have been described in patients with rheumatic diseases treated with tumor necrosis factor (TNF)-α inhibitors. Only another case of a patient receiving infliximab for CD who developed a B2 thymoma has been previously published (4).
Thymic tumors are a rare, albeit heterogeneous, group of malignancies with a broad range of clinical presentations. Thymoma is the most frequent subtype with an estimated incidence of 0.13-0.32/100,000/year and accounting for 0.2-1.5% of all malignancies (1, 5). Thymomas are associated with autoimmune diseases far more often than other malignancies which is not surprising due to the pivotal role of the thymus in shaping the immune system and fine-tuning the immune responses during early stages of life. Although the exact mechanisms underlying the development of autoimmune diseases in patients with thymoma are not yet fully elucidated, it is well established that perturbances of the thymic microenvironment alongside reduced expression of autoimmune regulator gene and major histocompatibility class II lead to a reduction of regulatory T-cells and as a consequence to an impaired immune tolerance (6). Regarding inflammatory bowel diseases, thymoma rarely occurs in patients with these conditions. Available studies have reported that ulcerative colitis was combined with thymoma in 0.3% of patients whereas the burden of thymoma in CD is unknown (7-9).
Myasthenia gravis (MG) may occur in up to 40% of patients with thymoma and, therefore, is the most frequently observed autoimmune disease (6). B1 and B2 thymomas are the histological subtypes most frequently associated with MG, but MG was also described in patients with AB thymoma and patients with thymic conditions other than thymoma such as thymic follicular hyperplasia or thymic atrophy

(6, 10). MG results from autoantibody-mediated damage at the neuromuscular junctions selectively targeting acetylcholine receptors and is characterized by clinical features including weakness and fatigability in skeletal muscles (11). The role of TNF-α in the pathogenesis of MG has been extensively investigated and in the past, the possible application of TNF-α blockers for MG treatment was also put forward (12, 13). However, the evidence that TNF-α serum levels broadly vary in patients with MG and are not correlated with the clinical picture, as well as the demonstration that MG may be induced by TNF-α blockers used for other indications dampened the enthusiasm towards this putative new treatment for MG (14-17).

**Conclusions**

In conclusion, the case that we presented raises some important questions that remain open and deserve to be addressed in the future. First, whether the patient developed the thymoma due to long-term immunosuppression with TNF-α inhibitors or whether he would have developed this neoplasm regardless of the therapy. Second, whether the type of TNF-α inhibitor may have played a role in the development of thymoma since it occurred 8 months after starting golimumab (no evidence of the lesion on the chest X-ray performed at adalimumab withdrawal). Third, whether the thymoma developed due to the concomitant presence of r-axSpA/CD and finally whether the patient did not develop MG because he was within the 60% of patients with thymoma that do not develop MG or because the long-term treatment with TNF-α inhibitors may have exerted some sort of protection towards autoimmunity.

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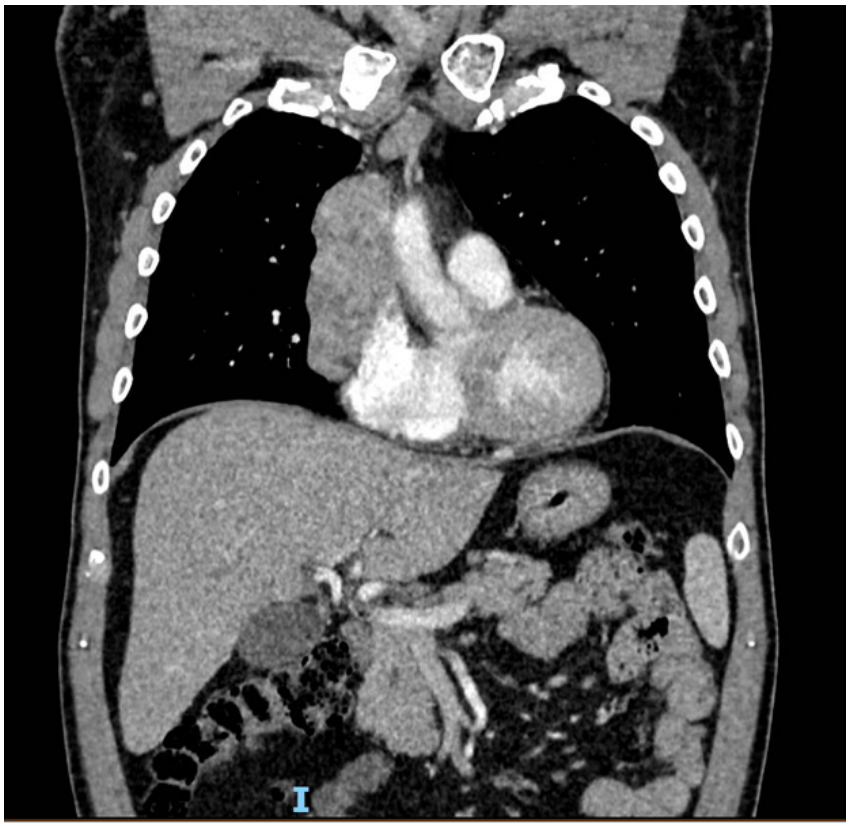

**Figure 1. Computed tomography scan showing the mediastinal mass.**