Association between anti-dsDNA titre increase and thymoma relapse

Sirs,

Thymoma is frequently associated with paraneoplastic syndromes such as myasthenia gravis (MG) (1). Moreover, in these patients rheumatic conditions or immunological abnormalities may also occur (2, 3). In this letter we describe an atypical case of relationship between thymoma appearance/relapse and anti-dsDNA antibodies occurrence in a patient diagnosed with undifferentiated connective tissue disease (UCTD).

In January 1996, a 29-year-old man presented with erythematosus cutaneous lesions on right arm and butterfly rash. Right arm skin biopsy showed vessel wall fibrinoid necrosis, infiltration of polymorphonuclear leukocytes in the dermis and in perivascular areas; lymphohystiocytes and rare eosinophils were also present, being consistent with leucocytoclastic vasculitis. Antinuclear (ANA), with a titre of 1:640 and homogeneous pattern in indirect immunofluorescence (IFI), and anti-dsDNA antibodies (1:40 in IFI, 189 UI/ml by ELISA) were positive. No other symptoms suggestive of SLE were present. Moreover, anti-ENA, anti-cardiolipin and anti-Beta2 glycoprotein1 were negative. Complement levels were normal as well as creatinine serum levels, urynalisis, leukocyte count and haemoglobin levels. According to clinical findings and laboratory results, a diagnosis of UCTD was made and prednisone therapy was started (25 mg/day) leading to remission of the cutaneous findings. Routine chest x-rays showed mediastinal enlargement; the subsequent computed-tomography (CT) evidenced a single lesion suggestive of thymoma. A thymectomy (Tx) was performed in April 1996; the histology evidenced an encapsulated thymoma predominantly composed of lymphoid cells (Masaoka Stage-I, WHO class-B1) (4, 5). After Tx, anti-dsDNA titre normalised (<1:10 in IFI, 18 UI/ml by ELISA) whereas ANA positivity was confirmed (1:320 with homogeneous pattern in IFI). Prednisone was tapered and withdrawn in July 1997. In January 1998, anti-dsDNA were again positive (1:40 IFI, 174 UI/ml ELISA) without clinical correlates. Thymoma relapse was evidenced at control chest-CT; the patient was then treated surgically again and histology confirmed the diagnosis. Anti-dsDNA were not detected at the follow-up control after Tx (<1:10 IFI, 12 UI/ml ELISA). In April 1999, because of a presentation with palpebral ptosys, disphagia, dislalia and muscle fatigability together with anti-acetylycholine-receptor-antibody (AchR-Ab) positivity, a diagnosis of MG was made; azathioprine (150 mg/day) and pyridostigmine were started with symptom remission. Thymoma relapse was subsequently evidenced by CT; anti-dsDNA titre concomitantly increased (1:40 IFI, 162 UI/ml ELISA). The patient was surgically treated and anti-dsDNA normalised (<1:10 IFI, 8 UI/ml ELISA); thymoma histology did not show any progression to a malignant type. Azathiopine was stopped in February 2004 because of MG remission and persistent negativity of AchR-Ab. In April 2004 anti-dsDNA increased again (1:40 IFI, 198UI/ml ELISA) and another relapse of thymoma was observed by CT, leading to a further surgical intervention and histology confirmation; anti-dsDNA disappeared again after Tx. Moreover, azathioprine was restarted in June 2004, and maintained up to the last follow-up visit. No further relapses of thymoma, UCTD, MG and cutaneous vasculitis have been observed eversince; anti-dsDNA were constantly negative, whereas ANA titre and pattern did not vary over time. Of note ANCA, anti-ENA, anticardiolipin, antiB2glicoprotein I were constantly negative and no other findings of connective tissue disease were observed during this long-term follow-up. Patient history is resumed in Figure 1.

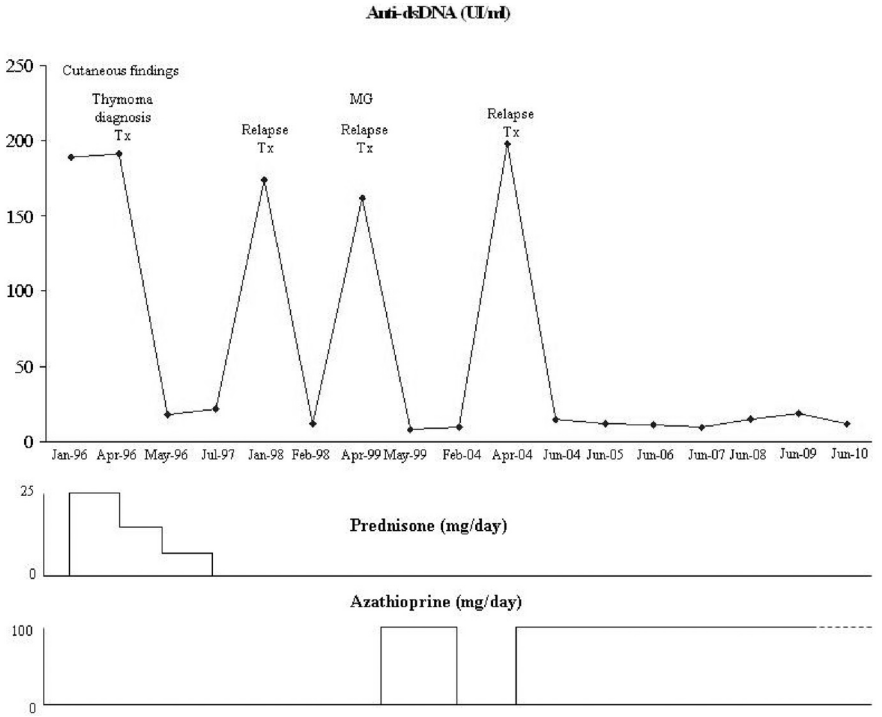

Fig. 1. Anti-dsDNA titre fluctuations overtime and clinical/therapeutic correlates; Tx: thymectomy, MG: myasthenia gravis.

The estimated prevalence of connective tissue diseases such as SLE in thymoma patients is about 2–7.7% of cases (6, 7). Moreover, as previously described, Tx in MG patients may induce the appearance of ANA (up to 45% of cases) and of high titre anti-dsDNA antibodies (201.4±61.2 Ui/ml) (8), the latter being found in up to 20% of MG patients (7). In the general literature, the data showed that Tx is a possible risk factor for both the development and relapse (6, 8, 9) of systemic autoimmune disorders/abnormalities in patients with MG or thymoma. On the contrary, the key point of the letter is that in our case anti-dsDNA titre increased concomitantly to thymoma appearance and relapses, normalising after Tx. Our observation suggests that the effects of thymoma and Tx on autoimmunity are heterogeneous and not completely understood. We first described a close relationship between thymoma and the occurrence of an autoantibody other than AchR-Ab (10). Finally, we observed in the same patient three different paraneoplastic syndromes/manifestations: cutaneous vasculitis, MG with AchR-Ab and UCTD with anti-dsDNA antibodies positivity; in fact the association of more than one paraneoplastic syndrome/manifestation is not frequently described (11).

In conclusion, although the relationship between thymoma and autoimmunity is well established, several questions still remain to be answered.

L. CAVAGNA, *MD*
E. PRISCO, *MD*
C. MONTECUCCO, *MD*
R CAPORALI, *MD*

Division of Rheumatology, University and Foundation IRCCS Policlinico S. Matteo, Pavia, Italy.

Address correspondence to:
Elena Prisco, MD, University and Foundation IRCCS Policlinico S. Matteo, P.le Golgi 2, 27100 Pavia, Italy.
E-mail: prisco.elena@libero.it

Competing interests: none declared.

References

1. TORMOEHLEN LM, PASCUZZI RM: Thymoma, myasthenia gravis, and other paraneoplastic syndromes. *Hematol Oncol Clin North Am* 2008; 22: 509-26.
2. EVOLI A, MINICUCI GM, VITALIANI R *et al*.: Paraneoplastic diseases associated with thymoma. *J Neurol* 2007; 254: 756-62.
3. BOZZOLO E, BELLONE M, QUARONI N, VOCI C, SABBADINI MG: Thymoma associated with systemic lupus erythematosus and immunologic abnormalities. *Lupus* 2009; 9: 151-4.
4. MASAOKA A, MONDEN Y, NAKAHARA K, TANIOKA T: Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981; 48: 2485-92.
5. ROSAI J, SOBIN L: Histological typing of tumours of the thymus. *In*: WORLD HEALTH ORGANIZATION ed. *International histological classification of tumours*. Heidelberg: Springer. 1999: 1-16.
6. GENTY I, JEAN R, CRETEL E, DURAND JM: Lupus and thymoma. *Lupus* 2000; 9: 478-9.
7. STHOEGER Z, NEIMAN A, ELBIRT D *et al*.: High prevalence of systemic lupus erythematosus in 78 myasthenia gravis patients: a clinical and serologic study. *Am J Med Sci* 2006; 331: 4-9.
8. GERLI R, PAGANELLI R, COSSARIZZA A *et al*.: Long term immunologic effects of thymectomy in patients with myastenia gravis. *J Allergy Clin Immunol* 1999; 103: 865-72.
9. BOONEN A, RENNENBERG R, VAN DER LINDEN S: Thymoma-associated systemic lupus erythematosus, exacerbating after thymectomy. A case report and review of the literature. *Rheumatology* 2000; 39: 1044-6.
10. OGER JJ: Thymus histology and acetylcholine receptor antibodies in generalized myasthenia gravis. *Ann N Y Acad Sci* 1993; 681: 110-2.
11. LUCCHI M, VITI A, RICCIARDI R, MURRI L, MUSSI A: Four thymus-related sindrome in a case of invasive thymoma. *J Thorac Cardiovasc Surg* 2007; 134: 1376-8.