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 erythematous cutaneous lesions on the 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; lymphohistiocytes and rare eosinophils were also present, being consistent with leucocytoclastic vasculitis. Antinuclear antibody (AchR-Ab) positivity, a diagnosis of a presentation with palpebral ptosis, 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 erythematous cutaneous lesions on the 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; lymphohistiocytes and rare eosinophils were also present, being consistent with leucocytoclastic vasculitis. Antinuclear antibody (AchR-Ab) positivity, 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 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, urinalysis, 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 ptosis, dysphagia, disalacia and muscle fatigability together with anti-acyetylcholine-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. Azathioprine 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, 198 UI/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 ever since; anti-ANA titre and pattern did not vary over time. Of note ANCA, anti-ENA, anticardiolipin, anti-B2glicoprotein1 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.

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±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.

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