PAEDIATRIC RHEUMATOLOGY

ANTI-RNP ANTIBODY IN A CHILD WITH UNDIFFERENTIATED CARCINOMA AND NO EVIDENCE OF MIXED CONNECTIVE TISSUE DISEASE

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SUMMARY

We describe a young girl who presented with musculoskeletal symptoms and who was found to have high titres of antinuclear antibody with anti-RNP antibody. She was initially suspected of having mixed connective tissue disease, but ultimately was found to have metastatic undifferentiated carcinoma with an unknown primary site. This is a very uncommon malignancy of childhood and an association with anti-RNP antibody has, to our knowledge, not been described. The clinical significance of this finding is discussed.

KEY WORDS: Antinuclear antibody, Anti-RNP antibody, Autoantibodies, Malignancy, Childhood.

CASE REPORT

An 11-yr-old Caucasian girl initially presented to her GP with pain in her left knee which was worse after physical activity, and with occasional sleep disturbance. She had no joint swelling or stiffness. Her past history and drug history were uneventful. Examination was normal, but her ESR was 52 mm/h. She was referred to a general paediatrician because of persistent knee pain, a transient butterfly rash, general malaise, weight loss and considerably reduced physical activity. Examination revealed tenderness at the knee, over the left medial femoral condyle, but no synovitis.

Investigations: WBC 11.2 × 10^9/l, Hb 12.1 g/l, platelets 363 × 10^9/l, ESR 35 mm/h; antinuclear antibodies (ANA) positive (1/640 by indirect immunofluorescence on HEp-2 cells with a speckled pattern), antibodies to RNP positive (1/16 by Ouchterlony immunodiffusion).

She was referred routinely to the paediatric rheumatology clinic at British Columbia Children's Hospital with a presumptive diagnosis of mixed connective tissue disease (MCTD). However, she was admitted as an emergency (4 months after initial presentation to her GP) with excruciating pain in the right clavicle. She then had a 6 week history of night sweats and marked weight loss. She denied cough, dyspnoea, rashes, photosensitivity, Raynaud’s phenomenon, alopecia, dysphagia, sicca symptoms, mouth or nasal ulcers. There was a family history of thyroid disease and discoid lupus erythematosus (maternal cousins).

On examination, she was cachetic with a low-grade fever. There was localized rib tenderness and a hard mass over the medial right clavicle, but no lymphadenopathy. Locomotor examination was unremarkable and there were no skin, mucous membrane or hair changes.

Investigations: WBC 11.6 × 10^9/l, Hb 13.9 g/l, platelets 399 × 10^9/l, ESR 75 mm/h, LDH 1207 U (normal <700). ANA and antibodies to RNP were positive (1/1280 and >1/16, respectively), and antibodies to Ro, La, Sm, dsDNA and rheumatoid factor were absent. The chest radiograph, chest computed tomography and Tc99m bone scan were abnormal (Figs 1–3). Biopsies of the clavicle and mediastinal lymph nodes demonstrated an undifferentiated large cell carcinoma with positive markers for cytokeratin and carcinoepithelial antigen (CEA). Extensive investigation failed to reveal a primary site and serum assays for alphafetoprotein, ßHCG (human choriogonadotrophin), CEA and ferritin were normal. Both of her parents were negative for ANA, RNP, Ro, La, Sm and DNA antibodies.

After six cycles of chemotherapy (cis-platinum, ifosfamide, VP16), there was marked improvement in symptoms and a reduction in adenopathy on chest radiograph. Subsequent assays before chemotherapy cycles demonstrated a decreasing titre anti-RNP antibody (Table I). However, she subsequently deteriorated and died on 22 November 1993. An autopsy demonstrated disseminated carcinomatosis with extensive pulmonary lymphatic involvement. The primary site was undetermined, but pancreatic origin was thought likely.

DISCUSSION

Carcinoma of unknown primary origin is a common malignancy of adults and carries a poor prognosis [1]. In children, carcinomas account for only 1.8% of malignant tumours, the primary site is usually known and involves the head and neck [2]. This child had a very unusual malignancy, and although histochemical
stains suggested an epithelial origin, the primary site was unknown. MCTD is also an uncommon disease of childhood and encompasses elements of systemic sclerosis, systemic lupus erythematosus (SLE) and dermatomyositis in association with high-titre anti-RNP antibody [3]. Although the hallmark of MCTD, anti-RNP antibodies are not diagnostic and occur in other rheumatic diseases such as SLE [3]. Constitutional symptoms may be a feature of MCTD, but the severity of the weight loss, night sweats and debility in this child was not typical; bone pain and tenderness rather than arthritis or arthralgia are not features. She had no other specific symptoms or signs of MCTD, and despite high-titre anti-RNP antibody, this diagnosis could not be substantiated.

Fig. 1.—Chest X-ray demonstrated an expanded medial third of the right clavicle with sclerotic and lytic areas, bilateral hilar adenopathy and adenopathy in the superior mediastinum.

Fig. 2.—Computed tomography of the thorax showing expanded sclerotic/lytic mass in the right clavicle with spiculated calcification and periosteal reaction.

Fig. 3.—Bone scan showed multiple hot spots including the right clavicle, left proximal femur, left second and third ribs, right posterior ninth rib and T11.

Although the connection between autoantibodies and malignancy is well described with and without documented autoimmune disease [4, 5], the mechanism is unknown. It has been proposed that factors leading to the expression of autoimmune disease, autoantibodies and the induction of oncogene expression might be shared [4]. The incidence of epithelial carcinomas is increased in dermatomyositis, systemic sclerosis and MCTD in adults [4], but such
associations have not been described in children. ANA have been associated with both adult and childhood malignancy (particularly of epithelial and haematological origin) [5, 6], although other studies did not find this association when patients with malignancy were compared to age-matched controls [7, 8]. DNA and ENA (including RNP) antibodies are rarely identified in adult malignancy [5–7], although an association between anti-Ro and anti-La and lymphoma has been described [7]. Although ANA are associated with specific autoimmune or rheumatic diseases, they are not a useful screening tool for the diagnosis of childhood rheumatic diseases [9, 10] as they may be detected in children with non-rheumatic musculoskeletal pain (6–16%) [9], infection [11], leukaemia [12] and even in healthy children (2–8%) [13, 14]. In contrast, antibodies to dsDNA or ENA are not reported in children in the absence of a specific rheumatic disorder [7, 9, 10, 12, 14].

In our patient, we believe that ANA and anti-RNP antibodies are associated with the malignant tumour; this association has not, to our knowledge, been described previously. Other explanations are unlikely—she did not have an identifiable rheumatic disease and there was no suggestion of familial clustering of autoimmune phenomena in that her parents were negative for specific ANA. Chemotherapy resulted in clinical and radiological improvement coinciding with a falling titre and eventual disappearance of anti-RNP antibody. However, during her subsequent deterioration, the titres of ANA and anti-RNP antibodies remained persistently negative. The importance of these antibodies as tumour markers and prognostic indicators is unknown. In adult-onset hypernephroma and lymphoma, autoantibody titres (dsDNA and ANA) have been reported to fall with reduction of tumour load or in response to chemotherapy and immunosuppression [15], and in adult breast cancer, a poor prognosis is associated with the presence of ANA and SM antibodies [16].

This girl had a malignancy that is rare in childhood. However, her presentation was consistent with a malignant process and the positive anti-RNP antibody was misleading. This case illustrates that autoantibodies, even highly specific antibodies such as anti-RNP, are not diagnostic of rheumatic diseases. ANA may be found in association with malignancy, infection and in healthy individuals, and its presence should be interpreted in the context of the clinical presentation.

TABLE I

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REFERENCES