Systemic sclerosis, capillary leak syndrome and nasopharyngeal carcinoma: an unusual association or paraneoplastic manifestations?

Sir, Paraneoplastic disorders are cancer-associated syndromes that occur at a distance from the primary tumour or metastases [1–4]. They have been associated with a wide range of rheumatic symptoms and signs, and the relationships between them are both complex and intriguing as they include a variety of conditions, most of which have no features distinguishing them from idiopathic rheumatic disorders [1–4]. Paraneoplastic rheumatic syndromes may arise at the same time or after a diagnosis of malignancy, but may occasionally be the presenting feature of a malignant pre-cancerous disease [1–4].

The proposed pathogenetic mechanisms include the hypotheses that both the cancer and the paraneoplastic rheumatic symptoms are independent effects of a common factor, such as viral infection or drug exposure; that paraneoplastic rheumatic diseases are a direct effect of toxins produced by tumour cells; and that paraneoplastic syndromes are mediated by a hypersensitivity reaction due to the tumoural expression of antigens shared by the cells targeted by the autoimmune disease [5].

We describe here the case of a 61-yr-old man who was referred to the Internal Medicine Department of S. Anna Hospital in Como (Italy) because of progressive sclerodactyly and RP arising 4 months before admission.

Physical examination revealed severe sclerodactyly (Fig. 1A). The patient had a positive 1/320 titre of ANAs (speckled pattern), but anti-ENAs, the results of a complete blood count, tumoural markers, and liver and renal function tests were normal, as were those of lung function tests, chest radiography, high-resolution thoracic CT, barium oesophageal radiography and echocardiography. Colour Doppler echocardiography revealed mild pulmonary arterial hypertension (45 mmHg), and nail-fold capillaroscopy a sclerodermic pattern (Fig. 1B). The patient was diagnosed as having lcSSc, and monthly infusions of a prostacyclin analogue (iloprost) were started.

One month later, he was admitted to hospital because of rapidly progressing shortness of breath, profound sweating, leg oedema, severe fatigue and otalgia. His white blood cell count was 29 000/ml, haematocrit 56% and haemoglobin 19.1 g/dl, and there was a high titre of anti-EBV immunoglobulin G; all other blood levels were normal. Chest radiography, electrocardiography and echocardiography were normal, and an otorhinolaryngological examination did not reveal any pathological feature. A diagnosis of atypical ‘systemic capillary leak syndrome’ (SCLS) was made on the basis of the clinical and laboratory findings. High-dose prednisone (60 mg/day, subsequently gradually tapered) and furosemide (25 mg/day) were started, and the patient’s symptoms began to improve and resolved within 1 month (except for the otalgia).

One year later, his general condition and otalgia worsened. CT of the head and neck showed chronic cholesteatomatous otitis media. Antimicrobial therapy had no effect, and a subsequent nasopharyngeal biopsy detected a nasopharyngeal carcinoma with neck lymph node metastasis (T2 N2c M0). Radiotherapy (surgery and chemotherapy were ruled out) led to only partial tumour control. The patient’s symptoms (diffuse sclerodermatous skin involvement, particularly in the area of irradiation, RP and shortness of breath) are currently progressively worsening, and severe dysphagia has appeared.

A paraneoplastic syndrome is suggested by a number of clinical factors, but can only be diagnosed after the cancer has been recognized [1–4]; however, the late onset of skin thickening and RP justifies careful screening as it is known that RP presenting after 50 yrs of age can be associated with various tumours although, to the best of our knowledge, no association between SSC and nasopharyngeal carcinoma has been previously reported [1–4].

The patient also suffered from SCLS, which was first described in 1960 by Clarkson et al. [6] as a rare and often fatal disease caused by a sudden reversible increase in capillary permeability. It is characterized by recurrent episodes of hypovolaemic shock due to the leakage of plasma into the extravascular compartment, with accompanying haemo-concentration, hypo-albuminaemia and oedema [7–9], although our patient was diagnosed as having an atypical variant because of the absence of hypo-albuminaemia. The aetiology of SCLS is unknown, although viral infections may play a role, and it has been described in patients with solid tumours.

The main feature distinguishing tumour-associated and paraneoplastic rheumatic diseases is the fact that, in the former, surgical removal or pharmacological treatment of the cancer has no effect on the rheumatic symptoms, whereas it almost always leads to the disappearance of the symptoms in the case of paraneoplastic diseases [1–4]. Unfortunately, we could not verify this in our patients because radiotherapy led only to partial tumour control.

To the best of our knowledge, this is the first report of an association between SSC and SCLS in a patient with...
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Comment on: The mechanism for efficacy of eccentric loading in Achilles tendon injury: an in vivo study in humans

Sir, I read with great interest the recent paper by Dr Rees and co-workers evaluating the potential mechanism behind the efficacy of eccentric loading of the Achilles tendon [1]. I would like to congratulate the authors on their interesting approach since gender might well apply to eccentric training in athletes too. However, I disagree with the authors by stating that they published ‘the first article to examine why eccentric loading is successful as a therapeutic intervention for mid-substance lesions of the Achilles tendon’. Actually, four male and three female healthy volunteers were included in their pilot study. Therefore, I would raise the question whether healthy Achilles tendons necessarily react the same as tendinopathic tendons, which is suggested by some of the comments of the authors as seen in the aforementioned statement as well as in the somewhat misleading title: ‘…eccentric loading in Achilles tendon injury’. I do not believe that the conclusions drawn by the authors from their observations in healthy volunteers do necessarily apply to injured tendons too.

In fact, several different papers published address the aforementioned issue of the potential underlying mechanism of eccentric training in tendinopathy. In my view, one should discriminate acute effects of eccentric training (such as those tested in the recent study) in contrast to mid-term effects, such as after 12 weeks of eccentric training, in addition to the fact whether healthy or tendinopathic individuals were tested. From a mechanical point of view, a randomized-controlled trial involving 74 healthy volunteers found that a 6-week eccentric training programme results in changes of mechanical properties of the Achilles tendon [2]. As far as connective tissue turnover is concerned, 12 weeks of eccentric training in Achilles tendinopathy leads to a significantly increased collagen synthesis rate [3]. From a radiographic point of view, acute eccentric training in Achilles tendinopathy patients leads to an immediate 12% increase of the tendon volume on T2-WI with a concomitant 31% increase of the intratendinous signal [4]. Colour Doppler sonography has been applied in tendinopathy evaluating the extent of neovascularization entering the tendon. Interestingly, 12 weeks of eccentric training in tendinopathy has been reported to reduce the degree of neovascularization detected by either colour or power Doppler sonography [5]. In line, quantitative assessment of Achilles tendon microcirculation could reveal a significantly increased capillary blood flow at the point of pain in both insertional as well as in mid-portion tendinopathy [6]. Twelve weeks of eccentric training reduces the pathologically increased capillary blood flow without changes of tendon oxygen saturation [7]. In addition, Achilles tendon venous outflow is facilitated after 12 weeks of eccentric training. As far as the paratendinous tissue is concerned, eccentric-training programme performed daily over 12 weeks reduced the increased paratendinous capillary blood flow in Achilles tendinopathy by as much as 45% and decreased pain level based on a visual analogue scale [8]. Local paratendon oxygenation was preserved while paratendinous post-capillary venous filling pressures were reduced after 12 weeks of eccentric training, which appears to be beneficial from the perspective of microcirculation. In sum, several distinct mechanisms underlying the eccentric training in both healthy and injured Achilles tendons in an acute and mid-term setting have been published to date.

In addition, I would appreciate if the authors could speculate whether gender might play a role for their findings as well. Recently, 85 women were studied with the finding that Achilles tendon diameter was greater in active post-menopausal women [9]. Hormone replacement therapy appeared to ameliorate this effect on the tendon diameter. Achilles tendon microcirculation varies by gender [10]. Symptomatic female patients have similarly elevated tendon capillary blood flow compared with symptomatic male patients suffering from Achilles tendinopathy, but superior tendon and paratendon oxygen saturations and reduced post-capillary venous filling pressures indicate better tendon and paratendon Achilles tendon microcirculation in women. Based on these preliminary clinical data it would be worth studying the impact of gender on tendon properties in the various aforementioned perspectives, since gender might have an impact on biomechanical properties as well.

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