

Enthesitis and small cell lung carcinoma: a novel paraneoplastic syndrome not previously described

Sirs,

Paraneoplastic syndromes (PS) are a challenging expression of many malignancies, usually before their diagnosis or recurrence. This is a case of locally advanced small cell lung carcinoma heralded by enthesitis unresponsive to glucocorticoids and methotrexate, the first described case of a new paraneoplastic syndrome.

We describe the case of a 63-year-old patient, heavy smoker, who was referred to our Department due to persistent temporal headache and elevation of C-reactive protein (CRP: 2.5 mg/dl). Pain was irradiated to neck and shoulder and associated to arthralgias, fever, weakness and scalp dysesthesia. Non-steroidal anti-inflammatory drugs (NSAIDs) and amitriptyline were ineffective.

Suspecting temporal arteritis, we performed temporal artery biopsy (negative), and prescribed prednisone, while laboratory tests showed positivity of rheumatoid factor (RF: 19 UI/ml) and antinuclear antibodies (1:640 speckled).

Steroid therapy was only slightly effective in reducing cranial symptoms and prednisone tapering led to further increase of CRP (6.9 mg/dl) and worsening of arthralgias at knees, elbows and ankles.

Thus, we performed musculoskeletal ultrasonography (US), which showed bilateral patellar tendon enthesitis, bilateral Achilles tendinitis and retrocalcaneal bursitis. Suspecting enthesoarthritis, we performed an intra-articular injection of triamcinolone and prescribed methotrexate, but no efficacy was reported.

In order to exclude a paraneoplastic syndrome, we eventually asked positron emission tomography/computed tomography scan, which showed a wide hypermetabolic focus in the upper lobe of the left lung (SUV 9).

Bronchoscopy and biopsies were eventually performed, with histological evidence of infiltrating small cell lung carcinoma (Ki67/MIB1 index 80%).

PS comprise a large number of signs and symptoms occurring during, before or after the diagnosis of a malignancy, involving organ and sites not primarily invaded by the tumor. The aetiology is usually unknown but

may be related to the activation of the immune system and to growth factors secreted by the neoplasm.

PS may be systemic or involve single organs or system. Rheumatic PS may present as arthropathies, muscular disorders, vasculitis, scleroderma, fasciitis and many other conditions (1-3).

Distinguishing paraneoplastic arthritis (PA) from idiopathic arthritis is usually difficult and to date only 8 case series are reported in literature, for a total of 121 patients (4). The largest and most recent cohort was described by Kisacik *et al.* (5), who compared 65 patients with PA with 50 affected by early rheumatoid arthritis (RA). PA seems to affect older patients than RA, with a higher male:female ratio. The onset is often acute, presenting with an asymmetric oligoarthritis or polyarthritis, although monoarthritis are described too (6). Markers of inflammation are usually elevated, while RF and anti-citrullinated proteins are negative in the majority of the patients. PA, typically unresponsive to NSAIDs and glucocorticoids but only to the treatment of the primary tumour, is often associated with breast and lung carcinoma (7) and haematological malignancies (8).

Our patient met many of the features reported above, but significantly differs from the previous reported cases, since he suffered from a bilateral enthesitis documented by an elevated power Doppler signal. His condition was more similar to enthesoarthritis than RA, although RF was positive, and no one of the cases we found in literature reported an involvement of the entheses.

Interestingly, Hagiwara *et al.* (9) reported that, among 115 patients meeting CASPAR criteria, 4 developed malignancies after the onset of arthritis and 19 before. Unfortunately, this paper does not mention how many of those patients actually suffered from enthesitis rather than arthritis, so, to our knowledge, our patient remains the first reported and US-demonstrated case of paraneoplastic enthesitis, a possible new entity within the spectrum of rheumatic PS.

The correlation and coexistence of autoimmune and neoplastic diseases is an intriguing matter of debate (10), as demonstrated by the immune-related adverse events during checkpoint inhibitors therapy. The comprehension of the exact immunological mechanisms will shed new light on this topic, giving more precise tools for the management of such conditions.

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Competing interests: none declared.

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References

1. ALIAS A, RODRIGUEZ EJ, BATEMAN HE, STERRETT AG, VALERIANO-MARCET J: Rheumatology and oncology: an updated review of rheumatic manifestations of malignancy and anti-neoplastic therapy. *Bull NYU Hosp Jt Dis* 2012; 70: 109-14.
2. MANGER B, SCHEFF G: Paraneoplastic syndromes in rheumatology. *Nat Rev Rheumatol* 2014; 10: 662-70.
3. FAM AG: Paraneoplastic rheumatic syndromes. *Baillieres Best Pract Res Clin Rheumatol* 2000; 14: 515-33.
4. MANGER B, SCHEFF G: Rheumatic paraneoplastic syndromes—a clinical link between malignancy and autoimmunity. *Clin Immunol* 2018; 186: 67-70.
5. KISACIK, B. ONAT A. M. KASIFOGLU T *et al.*: Diagnostic dilemma of paraneoplastic arthritis: case series. *Int J Rheum Dis* 2014; 17: 640-45.
6. CANTINI F, NICCOLI L, NANNINI C *et al.*: Isolated knee monoarthritis heralding resectable non-small-cell lung cancer. A paraneoplastic syndrome not previously described. *Ann Rheum Dis* 2007; 66: 1672-74.
7. KANAJI N, WATANABE N, KITA N *et al.*: Paraneoplastic syndromes associated with lung cancer. *World J Clin Oncol* 2014; 5: 197-223.
8. AZAR L, KHASNIS A: Paraneoplastic rheumatologic syndromes. *Curr Opin Rheumatol* 2013; 25: 44-49.
9. HAGIWARA K, SUYAMA Y, FUKUDA K: Clinical experience in 115 patients with arthritis and/or enthesitis who met the classification criteria for psoriatic arthritis (CASPAR) within the last two years – possible association with malignant disorders. *Mod Rheumatol* 2016; 26: 625-29.
10. MANDAL S, PILE K, CHACKO RT, DANDA D: Malignancy and autoimmunity: causally or casually related? *Int J Rheum Dis* 2014; 17: 601-5.