

Paraneoplastic syndromes and inflammatory rheumatic diseases : Not everything that glitters is gold. The case of polymyalgia rheumatica.

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Editorial

The term “Paraneoplastic Syndromes” (P.S.) refers to all the signs and symptoms caused by cancer but which are not directly related to the tumor mass nor its metastases. It is estimated that up to 8% of patients with cancer may present a P.S. Its manifestations may appear at the same time, before or after cancer, and, by definition, they regress after its treatment [1].

Paraneoplastic rheumatologic syndromes have been repeatedly described in the literature, especially for dermatomyositis and vasculitis [2,3]. They are thought to be caused by a disturbance of the immune response [4,5] or to be a consequence of abnormal cytokine release (typical the case of the Vascular Endothelial Growth Factor, VEGF). When paraneoplastic rheumatologic syndromes are not synchronous to cancer, most investigators agree in highlighting that the expression of an occult cancer must become clinically evident within a determinate timeframe, that is no more than 2 years. Paraneoplastic rheumatologic syndromes are difficultly distinguishable from idiopathic, non paraneoplastic manifestations, even if are usually less responsive to therapy than are the idiopathic ones [4]. On the other hand, the patients with inflammatory rheumatic diseases have an increased risk of developing malignancies [6]. In fact, chronic inflammation per se is an important favoring factor : for example, in patients with Rheumatoid Arthritis (RA), Sjogren's Syndrome (SS) or Systemic Lupus Erythematosus (SLE), cancer risk is strictly related to disease activity [7]. Instead, the pathogenetic importance of the immunosuppressive and/or immunoregulatory drugs is not univocal [8,9].

The question as to whether an inflammatory rheumatic disease is a paraneoplastic syndrome or a differential diagnosis of malignancy problematic is anything but trivial. This is particularly intriguing for less specific findings, such as joint pain, or constitutional manifestations (i.e., fever, loss of appetite, weight loss, fatigue, general malaise). The possibility that cancer can favor the production of autoantibodies, identical to those present in some rheumatic diseases, is another confounding element [10].

The question is of particular relevance for Polymyalgia Rheumatica (PMR). PMR can be considered the most frequent inflammatory rheumatic disease in Caucasian persons older than 70 years [11]. Its diagnosis is based upon recognition of a clinical syndrome consisting of pain and stiffness in the shoulder and pelvic girdle and morning stiffness lasting at least 45 minutes [12]. Constitutional manifestations may be present. In absence of a specific diagnostic test, the diagnosis of PMR is

basically clinical [12,13]. The rapid response to low-dosed glucocorticoids (GCs) (<20 mg prednisone per day), represents an additional diagnostic confirmation element. However, several patients fail to achieve a complete response after few days and – on the other hand – some diseases can mimic PMR not only in the clinical features but also in a fast response to low-dosed systemic GCs. Some of these diseases fail to maintain the first positive response in a short time but others (solid or hematological tumors, for example) can do it [14]. Furthermore, some patients initially diagnosed with PMR may be reclassified as having a different disease during follow-ups, seronegative RA being the most common alternative [13,14].

In the clinical practice, we can have three diagnostic challenges:

1) The diagnosis of PMR is not correct. Failure to respond to GCs therapy or frequent relapses must be considered as elements of suspicion. Furthermore, the presence of not typical laboratory findings should also be considered as a warning: among these, macrocytic anemia [15] or bicytopenia [16]. In these cases, the diagnosis should be revised. Furthermore, PMR symptoms may also occur in patients with cancer [17]. In a systematic review recently published by Muller et al. [18], amongst other important topics, a short-term association between PMR and cancer (less than 6 to 12 months after PMR diagnosis) deserved important considerations. In these cases, PMR may represent a misdiagnosis (the patient had cancer and was diagnosed with a PMR), or it is possible that the two conditions coexist. According to the guideline suggestions regarding exclusion cancer before making the PMR diagnosis, PMR can be considered as a PS only when cancer is synchronous or following the diagnosis ;

2) During follow-up, PMR is reclassified as a different disease. Among older patients initially identified as PMR and evaluated extensively since the onset, more than 20% are subsequently reclassified as seronegative RA. Seronegative RA is the most common diagnostic alternative, but not the only one [14]. In these cases, the significance for PMR as a P.S. must be identified with that of the subsequently recognized disease. Seronegative remitting symmetrical synovitis with pitting edema (RS3PE) deserves separate considerations. RS3PE is an uncommon elderly-onset rheumatic condition, described for the first time by McCarty et al. in 1985, characterized by tenosynovitis of extensor tendons at the wrist and (less frequently) at the feet, rapidly responding to low-dosed GCs (5-10 mg prednisone for day, on average). The levels of VEGF are significantly higher in these patients than in controls, and its levels decreased after GCs treatment. It is estimated that no more than 10% of patients with PMR may have RS3PE. The

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association RS3PE + PMR must be considered a neoplastic warning [19,20] ;

3) The diagnosis of PMR is correct and no alternative diagnosis is found during follow-up. A rigorous diagnostic work-up must be performed before making the PMR diagnosis. This diagnostic work-up must consider some inexpensive tests such as a chest X-ray, a prostate specific antigen, an abdominal-pelvic and breast (in women) ultrasound examination. In patients with highest risk of having an underlying cancer, additional tailored investigations should be requested [21]. When cancer is then diagnosed during the follow-up of these patients, PMR can be considered a real P.S. .

Not all that glitters is gold, one might say.

Conflict of interest

The author declare no conflict of interest.

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