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REVIEW ARTICLE

Paraneoplastic syndromes with connective tissue involvement. "It's not always lupus!"

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Summary

Paraneoplastic syndromes (PNS) are remote effects of cancer that are, by definition, caused neither by invasion of the tumor or its metastases nor by infection, ischemia, metabolic and nutritional deficits, surgery or other forms of tumor treatment.

The purpose of the current review was to present the challenging elements of differential diagnosis in oncology, as they may represent the main clinical problem in a patient diagnosed with cancer, even though the complete knowledge of both their clinical aspects and pathogenesis remain quite poor. This review focuses on the paraneoplastic syndromes related to dermatology and rheumatology, as the most frequent manifestations come from connective tissues that might determine a patient to ask for consultation by a general practitioner.

Key words: dermatology, paraneoplastic syndromes, rheumatology

Introduction

PNS are defined as a group of symptoms and clinical signs that occur in cancer patients and involve systemic effects that take place remotely from the tumor. These signs are neither caused by invasion of the primary tumor or its metastases nor by infection, ischemia, metabolic and nutritional deficits, surgery, radiotherapy or any other forms of cancer treatments [1]. A PNS usually arises from biologically active substances such as hormones, hormone precursors or hormone-like substances. Also, another mechanism is modulation of the immune system via autoimmunity, immune complexes production or immune suppression, or even by still unknown mechanisms [2,3].

To recognize a PNS may be clinically crucial for many different reasons, the most important of which being that it can lead to early diagnosis of a previously undetected neoplasia. It may also dominate the clinical presentation and lead to errors regarding the origin and type of primary cancer, or even follow the clinical course of the underlying tumor. In this way, such symptoms may be useful in monitoring the course of the disease, similar to a neoplastic marker just like prostate specific antigen (PSA) level in prostate adenocarcinoma.

An increasing number of reports on paraneoplastic phenomena can be found in the international medical literature over the past few years, as explained by the availability of better diagnostic tools and more effective therapies that - by prolonging the survival of patients diagnosed with cancer - may promote the occurrence of neoplastic hormonogenesis.

The purpose of the current review was to present some of the main paraneoplastic clinical manifestations, useful to know not only by oncologists but also by general practitioners, because the rapid detection and immediate treatment of the underlying neoplasia may of-

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fer the best chance to stabilizing a patient and prevent further deterioration, if not even the chance for cure.

Dermatology

Numerous cutaneous disorders have been associated with an underlying malignancy. In some cases the skin can be directly infiltrated by cancer cells that represent metastatic spread from an internal tumor, such as the Sister Mary Joseph nodule [4]. In other cases, skin lesions are related to the underlying presence of neoplasia, but don't contain malignant cells and are referred to as paraneoplastic dermatological syndromes. Some of them, such as Muir-Torre, Peutz-Jeghers or Cronkhite-Canada syndromes, are inherited and are caused by genetic factors. But others have unknown etiologies and unpredictable expression and prognosis [5].

Dermatologists have the advantage of recognizing certain cutaneous signs which may hint at a previously unknown malignancy and from a practical perspective such a skin manifestation has a very important diagnostic value if it is the sole expression of an otherwise asymptomatic carcinoma, leading to prompt diagnosis and treatment.

Many familial cancer syndromes have prominent dermatological features and very often the potential for a visceral malignancy is suspected after the skin disease is recognized. One such case is Gardner syndrome, an autonomic dominant disorder characterized by extensive adenomatous polyps of the colon and rectum. These polyps have a very high propensity for malignant transformation and are accompanied by extra colonic cancers, such as thyroid cancer, and also large epidermoid cysts, fibromas, lipomas, leiomyomas, trichoepitheliomas or neurofibromas. This condition, associated with adenomatous polyposis coli tumor suppressor gene, also include clinical features such as osteomas or congenital hypertrophy of the retinal pigmented epithelium [6].

Peutz-Jeghers syndrome, found to be related to mutations in the STK11/LKB1 gene on chromosome 19q13.3, is characterized by extensive hamartomatous polyps and carcinomas of the gastrointestinal tract, but also pigmented macules found on the lips, nose, buccal mucosa, fingertips and under the nails. But unlike the Gardner syndrome, malignant transformation of the polyps is rare. Cowden disease, also known as multiple hamartoma syndrome, is associated with trichilemmomas on the head, neck or even on the tongue and gingiva. These cutaneous signs appear together with fibrocystic disease of the breast, thyroid tumors or endometrial cancer [7,8]. The association of visceral carcinoma and numerous both malignant and benign sebaceous gland tumors can be found in the case of Muir-Torre syndrome, considered to be a subset of the hereditary nonpolyposis colon cancer syndrome. In the case of Birt-Hogg-Dubé syndrome, physicians associate skin tags and benign hair follicle tumors that most often appear on the head and neck with a high incidence of chromophobe and oncocytic types of renal or lung carcinoma, as well as spontaneous pneumothorax. Just like Birt-Hogg-Dubé's disease, a mutation of chromosome 17 also lead to another interesting malignancy: Howel-Evans syndrome [9].

Howel-Evans syndrome, first reported in two English families, describes benign tylosis and a high incidence of esophageal cancer, as well as oral leukoplakia. The thickened skin of the palms and soles develops during childhood, unlike the esophageal tumor that is delayed until middle age, a feature that makes upper digestive endoscopy a very effective screening method. Last, but certainly not least and a very well-known dermatological condition is neurofibromatosis type 1, known as von Recklinghausen disease. It includes axillary and inguinal freckling, cutaneous neurofibromas, plexiform neuromas and café-au-lait macules. These clinical features are complicated by malignant degeneration of the neurofibromas, multiple Schwann cell tumors, gastrointestinal stromal tumors and even bilateral pheochromocytomas. Genetic conditions may also include less frequent diseases, such as poikiloderma congenitale, ataxia-telangiectasia syndrome, Wiskott-Aldrich syndrome or Bloom syndrome, known for their inherited immunodeficiency [10,11].

Acanthosis nigricans is defined as a local, hyperkeratotic symmetric discoloration and verrucous lesions rarely involving the oral mucosa. These lesions are most often located on the face, elbows, axilla, knees and intermammary area, but also around the anus. Two forms are distinguished that may be either benign, congenital or acquired as a result of endocrinopathies, erythema nodosum or nicotinic urogastrone, or malignant, associated with cancer of various organs. Such cancers include adenocarcinomas of the abdominal cavity, thyroid, breast, esophagus or even sarcomas [12,13]. Acanthosis nigricans is also associated with other paraneoplastic conditions, such as Leser-Trelat symptom, paraneoplastic pemphigus or necrolytic migratory erythema. Ulysse Trelat was the first to propose that multiple seborrheic keratoses are associated with visceral malignancies [14,15]. This pathology presents with a sudden increase in the number or size of these multiple seborrheic keratoses, while no evidence of dermatitis or erythroderma proceed the features, with pruritus being the leading symptom in most cases.

Apart from less common PNS, such as Cronkhite-Canada syndrome or paraneoplastic hypertrichosis

lanuginosa acquisita, special attention should be paid to the Bazex syndrome. This disease, also known as acrokeratosis paraneoplastica, is actually a dermatosis characterized by acral psoriasiform lesions, characteristically seen in men and most commonly associated with squamous cell carcinoma of the upper aerodigestive tract or metastases to the cervical region [16].

Rheumatology

The musculoskeletal system can be affected by direct invasion of the primary tumor, metastasis, synovial reaction to juxtaarticular masses and also indirectly, by the effects of a distant tumor. This latter, referred to as a paraneoplastic syndrome in rheumatology, is thought to be the result of humoral mechanisms, the diagnosis of which is challenging in the absence of known malignancy.

Among the paraneoplastic rheumatic syndromes, hypertrophic osteoarthropathy, carcinomatous polyarthritis, myositis and vasculitis are the most frequently recognized. Musculoskeletal manifestations of malignancy may coincide, follow or antedate the diagnosis of cancer. The clinical manifestations of paraneoplastic rheumatic syndromes generally parallels that of primary tumors [17].

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by excessive proliferation of the skin and bone, involving the distal phalanx nail convexity, also known as clubbing. In most instances, HOA is a manifestation of a disease often localized in the chest [18]. A lot of patients with HOA are asymptomatic, but the ones with lung cancer usually have pain. Bone thickening may be appreciated in areas of the extremities not covered by muscles. Primary hypertrophic osteoarthropathy, also known as pachydermoperiostosis, is a rare genetic disease but secondary pachydermoperiostosis is cited as hypertrophic pulmonary osteoarthropathy and is associated with lung diseases, such as lung adenocarcinoma [19,20].

Carcinomatous polyarthritis is an inflammatory seronegative arthritis associated with malignancy. The differential diagnosis is broad and includes infectious diseases (i.e. Lyme disease or chlamydia), crystal-induced arthropathy, reactive arthritis, autoimmune diseases (i.e. systemic lupus erythematosus or rheumatic fever), or even connective tissue disorders or spondyloarthritises [21,22]. However, certain features suggest this form of arthritis, such as the explosive onset of asymmetric osteoarthritis or polyarthritis, predominant involvement of the joints of the lower extremities, late age of onset, sparing of wrists and hands, absence of rheumatoid factor, nodules, erosions and a positive family history of rheumatoid arthritis. Arthritis usually occurs in women with carcinoma of the breast and in men with carcinoma of the lung.

As carcinomatous polyarthritis is a diagnosis of exclusion, it lacks the other systemic manifestations that characterize these disorders, such as neurological involvement, mucocutaneous lesions, claudicating, Raynaud's phenomenon, renal involvement or gastrointestinal complains. It also lacks the association with antibodies such as anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anti-Smith or anti-centromere antibodies [23]. The clinical manifestations improve with the resection of the neoplasm and usually reappear with its recurrence. This disease may respond to NSAIDS and intra-articular glucocorticoids [17].

Determining whether musculoskeletal symptoms are caused by a rheumatic disease or a malignancy is complex and intriguing. Special attention must be paid to polymyalgia rheumatica. This is a clinical syndrome characterized by pain and stiffness in the neck, shoulders and hips, fatigue, weight loss and low-grade fever [24]. Nevertheless, it is rarely presented as a PNS manifestation, unlike the association of cancer and vasculitis.

Just like other PNS, cutaneous vasculitis can be the consequence of infections, hypersensitivity, rheumatic and autoimmune diseases. Vasculitides associated with malignancy are mainly cutaneous leukocytoclastic vasculitis, polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyangiitis, Wegener's granulomatosis and Henoch-Schönlein purpura [25]. Cutaneous manifestations of paraneoplastic vasculitis are polymorphic and non-specific, involving papules, nodules, bullae, purpura, ulcerations and necrotic lesions, unlike articular or other systemic manifestations that are more rarely observed. Usually, paraneoplastic vasculitis fails to respond to treatment with prednisone and improves with effective treatment of cancer. In addition, recurrence of such signs often occur with progression or metastases of cancer. A interesting systemic vasculitis is Henoch-Schönlein purpura, involving the small vessels of the skin, gastrointestinal tract and glomeration, as well as arthralgia or arthritis. Its main histopathology features are leukocytoclastic vasculitis mainly in papillary dermis, revealed with haematoxylin-eosin staining. It also includes vascular deposits of immunoglobulin A and complement 3, seen with direct immunofluorescence [26]. It should be said that hematological malignancies are 3-5 times more common than solid tumors when talking about paraneoplastic vasculitis [27], with pathophysiology mechanisms including decreased immune complex clearance or abnormal production of antibodies and tumor neoantigens leading to the formation of immune

complexes that deposit within the blood complexes. It also includes similarities between tumor antigens and endothelial cell antigens, deregulated lymphocytes that cause a switch from IgM to IgA isotypes and aberrant inflammatory cytokines produced either by malignant tumor cells or through the tumor microenvironment [28].

Cancer is detected in approximately one third of cases with dermatomyositis, in 15% of poliomyelitis, with over half of the tumors diagnosed after the initial diagnosis, out of which the majority within one year time difference. The mechanism involved is linked to autoimmunity, that may arise in the setting of a result of immune responses to mutated forms of self-antigens generated in nascent cancer cells. This will subsequently lead to the targeting of wild-type forms of the proteins in non-transformed cells [29]. Although tantalizing, to prove this theory of paraneoplasia is difficult and requires the identification of myositis-specific antigens (MSA)-specific T cells, capable of lysing tumor targets both in patients with myositis and in those with related neoplasia who do not develop myositis. It is also important to determine whether anti-MSA immunity develops over time in the setting of tumorigenesis in large prospective population-based studies [30].

Conclusion

At the time of presentation of the skin or joint symptoms, most patients have not yet been diagnosed with cancer and the detection of paraneoplastic signs can help diagnose the obvious syndrome and may direct the search for an underlying neoplasm. On the other hand, in a patient known to have cancer, the presentation of a PNS may herald recurrence of the tumor or of a second tumor, after metastatic complications have already been ruled out.

The rapid detection and immediate treatment of cancer so often appears to offer the best chance of stabilizing the patient and prevent further deterioration. Thus, as the American College of Rheumatology suggests, a skin or musculoskeletal manifestation does not always direct to the most obvious diagnosis such as systemic lupus erythematosus. Sometimes a more thorough analysis is required, an analysis that might represent the difference between life and death in some cases.

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