Cutaneous vasculitis and cancer: A clinical approach

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Introduction

Paraneoplastic syndromes are those syndromes associated with malignancy that occur at a distance from the primary tumor or metastases. They are cancer-induced by means of hormones, cytokines, immunoglobulins, or other humoral mediators, not all of which have been identified yet. Cutaneous vasculitis (CV) comprises a broad and diverse group of diseases characterized by predominant involvement of the skin with histopathologic findings that have vascular inflammation and blood vessel damage in common, especially leukocytoclastic vasculitis (1). It is generally a benign and self-limited condition confined exclusively to the skin (2). However, CV may occur in patients with systemic necrotizing vasculitis or other entities such as infections or connective tissue diseases (3-5). Cutaneous vasculitis may also be associated with malignant disorders and behave like a paraneoplastic syndrome (6-11).

There are no specific indicators to raise the suspicion of the possible presence of a malignancy in patients with CV. For these reasons several points can be made about diagnosis of this condition:

1. In the presence of typical clinical manifestations, CV can be diagnosed in a straightforward fashion by expert clinicians who often see this condition (2).
2. In series of patients with CV, an association with other diseases has been observed.
3. Cutaneous vasculitis limited to the skin is remarkably predictable in its rapid and sometimes complete improvement after bed-rest (12) and in some cases with low-dose prednisone.
4. In typical cases an extensive work-up for tumor or infections is not needed.
5. Nevertheless, in view of the lack of specific diagnostic tests, the clinician should remain alert to the possibility of another disease presenting with CV and follow up clues to the presence of another disease when present.

The actual proportion of patients with CV and malignancy is not well defined and may vary in different populations. Sanchez-Guerrero et al. reported 11 cases of paraneoplastic vasculitis among 222 patients presenting with vasculitis. The majority of patients had CV and leukocytoclastic vasculitis was histologically confirmed (9). In 3 cases the CV preceded or was the presenting manifestation of neoplasia. However, no information about the actual proportion of paraneoplastic small-vessel CV was available in their study as no data about the number of cases presenting with only small-vessel CV among the 222 patients was given. In this respect, 2 of the 11 cases with paraneoplastic vasculitis also had medium-sized vasculitis.

In another report malignancy was not observed in 82 patients with CV (13). In contrast, an underlying neoplasm was found in association with CV in 8% of 101 cases with CV (14). In the unsolicited series of adults with biopsy-proven vasculitis from Lugo (Spain), that included not only small-sized vasculitis but also middle and large-sized vasculitis seen in that region between 1988 and 1997, paraneoplastic CV was observed in 8 of the whole group of 267 patients (3.0%) (5). The absence of a previous selection of patients in this series along with the inclusion of all types of vasculitis and patients with typical syndromes may explain the low incidence of paraneoplastic CV found in that study. Of note, in all 8 cases and in another case observed in 1998, CV preceded the diagnosis of malignancy and there was a close temporal relationship between the cancer and CV (15, 16). Hutson and Hoffman have also recently described a close temporal concurrence of vasculitis and cancer (17). In keeping with previous reports (18), in the series from Lugo previous episodes of purpura prior to the diagnosis of malignancy were observed in 3 of the 6 patients with hematologic disorders. In most series hematologic disorders have been more commonly associated with CV than solid neoplasms (6, 7, 15). As discussed above, paraneoplastic vasculitis associated with myeloproliferative and lymphoproliferative diseases usually antedates the diagnosis of malignancy (8, 9, 18-20). However, in hairy cell leukemia paraneoplastic vasculitis presenting as CV or polyarteritis nodosa-like disease may occur after the diagnosis of the hematologic disorder (8).
Cutaneous vasculitis, in frequent association with refractory anemia with excess blasts, was the presenting manifestation in 7 of 162 patients with myelodysplastic syndrome (21). Multiple myeloma, mainly IgA, myelofibrosis, and T-cell lymphoma have also been reported in association with paraneoplastic vasculitis (8, 22-25). In addition, plasma cell dyscrasias, in special plasma cell myeloma, and non-Hodgkin’s lymphomas have frequently been associated with mixed cryoglobulinemia (15, 26). The occurrence of small vessel CV leading to the diagnosis of an underlying solid malignancy has also been reported (6, 7, 11, 15). Lung, prostate, colon, renal, breast, head and neck (squamous cell), and endometrial cancer are the most frequent non-hematologic neoplasms associated with CV (10, 11, 15, 16).

In view of the above, we would suggest the following work-up to exclude an underlying malignancy in a patient presenting with CV (Fig. 1).

A) A clinical history should be taken. The interview should elicit data regarding the following:
1. Duration of symptoms with special reference to previous episodes of palpable purpura.
2. Severe constitutional syndrome including unexplained asthenia, anorexia and weight loss.
3. Previous history of drug intake that may be responsible for the development of CV.
4. To exclude symptoms that may be related to the presence of a primary systemic vasculitis such as Wegener granulomatosis, polyarteritis nodosa, microscopic polyangiitis, or Churg-Strauss syndrome presenting with cutaneous manifestations, and connective tissue diseases, mainly systemic lupus erythematosus, Sjögren’s syndrome or rheumatoid arthritis.
5. Data about possible infections that may present with cutaneous manifestations.

B) Physical examination:
1. Fever may not be related to the tumor and in these cases systemic infections should be excluded.
2. The presence of visceral enlargement or lymphadenopathies should require a search for either solid or hematologic malignancies.

C) Laboratory analysis should include full blood counts, blood biochemistry including liver and function tests, protein electrophoresis, rheumatoid factor, antinuclear antibodies, and urinanalysis.
1. The presence of bicytopenia or severe anemia (< 100 g/l of hemoglobin) should lead to evaluation for hematologic malignancies. In these cases blood smear examination and bone marrow biopsy should be considered.
2. Unexplained hematuria should lead to studies for kidney or urinary collecting system malignancies.
3. If a monoclonal immunoglobulin in serum or urine is present, multiple myeloma and primary amyloidosis need to be excluded.

D) A chest radiograph should also be routinely performed as CV may be the presenting manifestation of lung cancer.

In summary, although malignancy associated with CV is uncommon, it should be considered in patients with unexplained vasculitis. Even though there are no specific clinical findings that are diagnostic of paraneoplastic vasculitis, the suspicion of this condition should be increased in the presence of severe constitutional symptoms, a chronic course of relapsing episodes of skin purpuric lesions, and especially in the presence of a hematologic abnormality.

References
Cutaneous vasculitis and cancer / M.A. González-Gay et al.

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