short report
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CUTANEOUS VASCULITIS IN NON HODGKIN'S LYMPHOMA

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ABSTRACT

Cutaneous vasculitis has been described in association with various hematological malignancies, but it seems to be very uncommon among non Hodgkin's lymphomas (NHL). For this reason no attention has been given to the peculiarity of this rare association. We identified 5 cases of cutaneous vasculitis among 315 NHL patients examined at our Institution from 1984 through 1990 and after the appearance of vasculitis, we observed some heterogeneity in either the degree of activity or in the clinical outcome of the NHL. The onset of cutaneous vasculitis appeared to mark two different clinical patterns: a vasculitis present from diagnosis characterized an indolent course of the neoplasia, while a late-appearing vasculitis was followed by rapid lymphoma progression and short survival.

Key words: vasculitis, non Hodgkin's lymphoma, prognosis, skin lesions, chemotherapy

Cutaneous vasculitis (CV) is a disease which may arise during the course of several disorders.[1,2] Among malignancies, the occurrence of CV in myeloid and lymphoid tumors has been reported,[3-11] but so far the exact mechanism and the clinical significance of this association are not known. We report here the histories of five patients affected by non Hodgkin's lymphoma (NHL) in whom CV appeared at different times with respect to the course of the malignancy.

Case reports

Among 315 NHL patients examined at our Institution from 1984 to 1990, we found five who presented CV. No cases of mycosis fungoides or Sezary's syndrome were included. Age ranged from 34 to 72 years (median 58); three subjects were males and two females. Besides the conventional hematological and biochemical tests, the following analyses (reported in Table 1) were performed for each patient: antinuclear antibodies, rheumatoid factors, complement fractions 3 and 4, hepatitis B and C markers, cryoglobulins.

Case 1

A female, aged 34 with NHL small lymphocytic type, stage III B, was diagnosed in July 1984. Treatment with four C-MOPP courses failed to determine any response, but subsequent chemotherapy with a CHOP-B (six cycles) schedule resulted in a partial remission (PR). In November 1987 NHL progression was diagnosed and concurrently the patient showed CV lesions. Aggressive chemotherapy (MACOP-B) was instituted, but she died three months later (February 1988) from disease progression.

Case 2

A 58-year-old woman, affected by NHL diffuse centrocytic/centroblastic type, stage IV B, was diagnosed in October 1984. Eleven courses of CVP determined a complete remission (CR) in July 1985. CV manifestations occurred while the patient was in CR almost one year later (May 1986), and were followed after five months (October 1986) by a relapse of NHL. She was then treated with six additional CVP courses but no tumor regression was achieved, and the cutaneous lesions showed only a partial resolution.

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Table 1. Laboratory data from the 5 NHL-CV patients.

Case	Hb g/dL	WBC ($x10^9$/L)	PLT ($x10^9$/L)	ANA	CRYO	RF	C3	C4
1	12.8	6.0	450.0	neg	neg	neg	normal	normal
2	12.1	6.9	180.0	neg	neg	neg	normal	normal
3	12.8	5.4	125.0	neg	N.D.	neg	normal	normal
4	13.8	27.0	174.0	neg	neg	neg	normal	normal
5	16.1	7.2	159.0	neg	neg	neg	normal	normal

ND: not determined; normal: C3=144±22 mg/dL, C4=30±20 mg/dL.

The patient died from lymphoma progression in June 1987.

Case 3

A male aged 41 with NHL follicular centrocytic/centroblastic type, stage III A, was diagnosed in April 1985. Treatment with six C-MOPP cycles determined a PR in October 1985. CV occurred in July 1989 and a month later NHL progression was observed along with a histologic change towards a high grade malignant lymphoma. The patient was started on second-line chemotherapy, a mitoxantrone-containing regimen (CNOP), but he showed no response to therapy and died three months later (October 1989) as a result of disease progression.

Case 4

A previously healthy male, aged 72, presented a CV in April 1989 and three months later was diagnosed has having a NHL follicular centrocytic/centroblastic type, stage III A. Nine CVP courses administered until October 1991 determined a PR and maintenance therapy with chlorambucil plus prednisone was given from in November 1991 to March 1992. The cutaneous lesions showed intermittent clinical behavior during the administration of chemotherapy. The patient is still in partial remission.

Case 5

A 63-year-old man with a small lymphocytic type NHL, stage IV B, was diagnosed in November 1989. CV manifestations were concurrent with diagnosis and prior to any therapy. Six courses of a CVP regimen determined a complete remission. CV appeared intermittently both during chemotherapy administration and after it was stopped. The patient has not needed any further chemotherapy.

In each case a clinical suspicion of vasculitis arose in the presence of palpable purpura and/or urticariod lesions. CV was always confirmed after excisional skin biopsies and leukemic cells were not identified in any specimen. Morphologic CV lesions appeared either as maculopapular eruptions (cases 1,2,3,5) or as urticariod aspects (case 4). Intense pruritus and a burning or stinging sensation often accompanied the dermatitis. At microscopic examination, a picture of necrotizing leukocytoclastic vasculitis involving vessel walls and characterized by disruption of endothelial integrity and neutrophil infiltration was always evident. Perivascular mononuclear cell infiltration was also observed in two cases (cases 1 and 5).

Discussion

The association between CV and NHL was mentioned for the first time in 1965,[3] but so far the real incidence of this association has not been determined, nor has the issue of whether these cases could have some particular features ever been addressed. In our study we found an incidence of more than one case of vasculitis per one hundred NHL (5/315 patients, 1.58%). This frequency is higher than that found by Greer *et al.*,[4] who reported a cumulative incidence of 0.45 %, but among various hematological malignancies. In fact, in Greer's series only two cases of CV associated to lymphoma were described; the majority of those cases were affected by myeloid neoplasias.

Because of our larger series, we were able to observe some heterogeneity in the clinical

course of these patients and we identified two groups who differed as to: i) the temporal relationship between CV appearance and diagnosis of NHL; ii) the outcome of the lymphoma with respect to CV onset. In two patients (cases 4 and 5), CV arose prior to or concurrently with NHL and did not seem to be influenced by NHL activity, as indicated by the intermittent appearance of the cutaneous lesions after chemotherapy had determined a substantial cytoreduction of the neoplastic mass. In these patients the lymphoproliferative disease had an indolent clinical course, and CV was well controlled by low doses of corticosteroids. In the second group (cases 1, 2, 3) CV arose late during the course of the lymphoma and was always followed by neoplastic disease progression or relapse. It is noteworthy that in this latter group the NHL became resistant to chemotherapy after the appearance of CV. This difference in clinical course stimulated us to speculate whether CV might have a different significance in the two groups of patients.

A condition of immunodysregulation is known to underlie both CV and NHL development.[4,5] Hence it might be hypothesized that CV and NHL could be found in the same patient as the result of a common facilitating factor, without the need for a direct pathogenetic relationship between the two diseases. The clinical course of vasculitis observed in the first group of patients fits this hypothesis. In the second group, however, the clinical behavior of both CV and NHL would suggest that cutaneous manifestations arising late during the course of NHL could be closely linked to an aggressive phase of the lymphoproliferative disease. This might be explained either as a clinical condition of host hypersensitivity to tumor constitutive antigens, or as a major host reaction against new tumoral ones.[4] Furthermore, chemotherapy could have played a role in determining appearance of CV, although the cutaneous lesions were strictly linked to lymphoma progression or relapse. Alternatively, a change in cytokine production might also be involved.[12,13] Unfortunately, we were not able to perform cytokine assays at the time of the observations.

In conclusion, from our preliminary clinical investigation it would seem that when CV appears late during the clinical course of a NHL, an aggressive phase or an impending relapse of the lymphoid neoplasia may be expected, and a possible histological conversion should also be actively pursued, whereas when CV precedes the lymphoid neoplasia it may not signal a poor prognosis. However, further clinical observations are required to better understanding of the immunopathogenetic links between the two diseases.

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