Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases

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ABSTRACT

Background
Skin involvement is frequent in ALK-positive anaplastic large cell lymphomas. The role of an insect bite as a triggering event has been postulated but not well documented.

Design and Methods
We retrospectively investigated five cases of ALK-positive anaplastic large cell lymphoma who presented with skin lesions occurring after an insect bite. Biopsies were immunostained with antibodies against CD30, ALK, T- and B-cell antigens.

Results
Persistent skin lesions developed after solitary insect bites in three patients and after multiple bites in two. Regional lymphadenopathy developed within weeks after the bite in three cases. In four cases the correct diagnosis was delayed due to misinterpretation of the findings as a reactive infiltrate in the skin (n=2) or lymph nodes (n=2); all cases subsequently showed small numbers of cells with nuclear and cytoplasmic staining for ALK. The final diagnoses were lymphohistiocytic variant (n=3) and composite common/small cell type (n=2) anaplastic large cell lymphoma. The patients were treated and three were alive at the last follow-up. Two patients died, one of pneumonia and the other of disseminated disease.

Conclusions
In these cases the sequence of events between the insect bites and the occurrence of both skin lesions and satellite lymphadenopathy suggest a direct relationship between the bite and the presentation with anaplastic large cell lymphoma. We postulate that insect bite-associated antigens could result in an influx of T lymphocytes, some bearing the t(2;5). The subsequent release of cytokines at the site of the bite could act as a 'second hit', eliciting activation of the latter cells, which would then express the oncogenic NPM-ALK protein and undergo uncontrolled proliferation.

Key words: ALK-positive ALCL, NPM-ALK, skin involvement.

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Introduction

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is recognized as a distinct entity in the 2008 World Health Organization (WHO) classification of malignant lymphomas.[1] The majority of ALCL are associated with a reciprocal translocation, t(2;5)(p23;q35) which juxtaposes the gene at 5q35 encoding nucleophosmin (NPM), a nucleolar-associated phosphoprotein, with the gene coding for a tyrosine kinase receptor, ALK, at 2p23.[2] However, variant translocations involving *ALK* and other partner genes on chromosomes 1, 2, 3, 17, 19 and 22 have been described.[3] All result in abnormal expression of ALK chimeric proteins, with tyrosine kinase activity and oncogenic properties.[3] ALK fusion proteins can be detected with anti-ALK antibodies, which are of crucial diagnostic value to identify lesions that may resemble ALK-positive ALCL morphologically and phenotypically (i.e.CD30 expression, T/null phenotype), such as ALK-negative ALCL and some primary cutaneous CD30-positive lymphoproliferative disorders (i.e. primary cutaneous ALCL and lymphomatoid papulosis).[4-7]

ALK-positive ALCL are characterized by frequent extranodal involvement, notably skin involvement (reported in 20-30% of cases), which has a negative prognostic impact.[1,8] Given the broad morphological spectrum of ALK-positive ALCL, the diagnosis of ALCL presenting with cutaneous involvement is not always easy, a fact which explains the original histopathological diagnosis of "non-malignant inflammatory disease" in some cases.[9] Occasionally, the latter erroneous diagnosis may be suggested by a clinical history of an insect bite.[9] Interestingly, the role of an insect bite as an event triggering systemic ALCL has been postulated, although it remains controversial.[10] We report here five cases of systemic ALK-positive ALCL presenting at onset with skin lesions occurring after an insect bite.

Design and Methods

Between 1984 and 2007, five children with similar clinical and histological features were identified among a series of more than 400 patients with ALK-positive ALCL from different institutions. The clinicopathological features of one of these cases (n. 4) have already been reported.[10] All five children presented with a systemic ALK-positive ALCL occurring after an insect bite. Clinical data, including age at diagnosis, presenting symptoms, clinical stage of disease, treatment, and follow-up, were collected from the patients' charts. The diagnosis of ALK-positive ALCL was made from a skin biopsy in one case (# 3), both skin and lymph node biopsies in two cases (# 2 and 5) and from a lymph node biopsy in the two remaining cases (# 1 and 4). In case # 1, a lung biopsy was also performed because of pulmonary atelectasis. Hematoxylin and eosin (H&E)- and immunohistochemical-stained slides from archival material were reviewed and additional stains performed when paraffin blocks were available. For case # 5, immunostaining was performed on de-stained H&E sections as previously described.[11] Overall, in addition to monoclonal antibodies against CD30/BerH2 and ALK, most cases were immunostained for epithelial membrane antigen (EMA) and several T-cell (CD2, CD3, CD4, CD5, CD7, CD8, CD43) and B-cell markers (CD20, CD79a). Antibody binding was detected with Dako REAL Detection System (Code K5001).

Results

The patients' clinical features at presentation, diagnosis, treatment and follow-up data are summarized in Table 1. Three patients were male and two female and they ranged in age from 7 to 11 years old. They received solitary (cases # 1, 3, and 4) or multiple insect bites (cases # 2 and 5). Four of them (cases # 1, 2, 3, 5) presented with persistent or growing skin lesions at the site of the bite. Satellite lymphadenopathy developed a few weeks after the bite in two cases (cases # 1 and 2). In one case (# 4), supraclavicular lymphadenopathy, which occurred 1 month after a neck bite, was the presenting symptom. All patients received antibiotics or steroids with no response in four cases (# 1, 2, 3 and 4) and a partial response in one case (case # 5). Four patients had fever at the time of diagnosis and two of the patients' general condition deteriorated with weight loss, asthenia, and pulmonary signs (cases # 1 and 4). In one case (# 4), the nature of the insect bite was clearly identified as being a tick bite on the neck 1 month earlier with a positive test for Rickettsia. A tick bite was also suspected in case # 1 but no serological testing was performed. In case # 3, the skin lesions appeared, according to the patient's family, after a wasp bite and in the two remaining cases (# 2 and 5) the nature of the insect bites remained undetermined. However, the clinical history of case # 5 left no doubt regarding the crucial role of insect bites in the presentation of the disease. Briefly, this 9-year old white male went on a camping trip in May 1984 with his boy scout troop. He received multiple insect bites. Most of these resolved but 2-3 weeks later he developed new lesions, up to the size of 2 cm, on his back and neck. After a course of steroids, all the lesions resolved except one on the left flank. The lesion was biopsied and a diagnosis of "non-specific reactive infiltrate" was originally made (Figure 1A). After the first biopsy, the lesion did not heal and progressively enlarged. A new skin biopsy was performed in February 1985 and led to the diagnosis of "large cell immunoblastic lymphoma". Approximately 1 week later the patient underwent surgical resection of a left axillary lymph node which enabled the diagnosis of lymphoma to be confirmed (Figure 1C-D).

Except for case n. 4, previously reported,[10] all the other cases were observed before the availability of anti-ALK antibodies and only CD30 and EMA stains were initially performed.[4,5] All skin and lymph node biopsies were re-examined. In addition to CD30 and EMA, ALK staining and several T- and B-cell markers were used. In case n. 1, the lymph node lesion originally interpreted as lymphadenitis rich in macrophages proved to be an ALK-positive lymphohistiocytic ALCL (Figure 2A). Scattered CD30 and EMA-positive cells were also positive for ALK protein (Figure 2B). Some large atypical cells with "hallmark cell" features were associated with a small cell component showing nuclear-restricted ALK staining. A few months later, the patient developed pulmonary symptoms with cough and atelectasis secondary to a bronchial tumor diagnosed as "Ki-1 lymphoma" (i.e. $CD30^+$). This lesion consisted of a pure population of large basophilic cells (i.e.

hallmark cells) that met the criteria of ALK-positive common type ALCL. Comparable features were observed in the supraclavicular lymph node biopsy from case n. 4 in whom lymphadenopathy appeared after a tick bite on the neck 1 month earlier (Figure 2C). The diagnosis of "hyperimmune reaction" was made initially, but despite steroids and antibiotics, the patient's general condition deteriorated rapidly in association with liver and spleen enlargement. Chest X-rays showed a mediastinal mass with pulmonary failure.[10] Finally, the diagnosis was revised to ALK-positive lymphohistiocytic ALCL (Figure 2D). A small cell component was also noted in this case after ALK staining (Figure 2D).

All patients presented with skin lesions that were clini-

Table 1. Clinical features, histopathologic diagnosis and follow-up of the 5 patients included in the study.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age at diagnosis (years)/Sex[a]	11/M	7/F	7/M	9/F	9/M
Recent insect bite history	July 1985 Insect bite (tick ?) on the right shoulder	March 1986 Undetermined insect bite on the wrist	October 1996 Clavicular wasp bite	December 1998 Neck insect bite (tick) (positive serological test for Rickettsia)	May 1984 Multiple insect bites
Presenting chief complaint	July 1985 Persistent skin lesion on the shoulder after insect bite associated with ipsilateral axillary lymphadenopathy	March 1986 Wrist skin lesions (n=3) June 1986 Axillary lymphadenopathy	January 1997 Supraclavicular subcutaneous mass at the site of wasp bite	January 1999 Supraclavicular lymphadenopathy	May 1984 Multiple skin lesions
Histopathological diagnosis	August 1985 Supraclavicular LN[b]: reactive lymph node September 1985 Axillary LN[b]: ALCL[c] Lymphohistiocytic pattern (later proved to be positive for ALK1) April 1986: lung atelectasis with bronchial tumor: "Ki-1 lymphoma"	March 1986 First skin biopsy: reactive lymphoid hyperplasia July 1986 Second skin biopsy and LN[b] biopsy: ALCL[c] Lymphohistiocytic pattern (later proved to be positive for ALK1)	January 1997 Subcutaneous mass: ALCL[c] Composite pattern (common plus small cell patterns) (later proved to be positive for ALK1)	January 1999 LN biopsy: reactive lymph node January 1999 Review of the LN[b] biopsy ALK-positive ALCL[c], Lymphohistiocytic pattern[d]	May 1984 First skin biopsy: reactive lymphoid hyperplasia, later shown to contain ALK+ cells February 1985 Second skin biopsy: "immunoblastic lymphoma" revised to ALCL[c] composite pattern (common plus small cell patterns) March 1985 LN[b] biopsy: ALCL[c] composite pattern[d] (later proved to be positive for ALK1)
B symptoms[e]	Fever, weight loss	Fever	Fever	Fever	No
Stage according to Ann Arbor classification	IV	IV (bone marrow positive)	II	I	II
Skin lesions at the time of ALCL[c] diagnosis	Yes	Yes	Yes	No	Yes
Time from insect bite to onset of disease	1 week	3 months	4 months	3 weeks	3 weeks
Treatment	Methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone Radiotherapy	Methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone	Methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone	Methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone	Multi-agent chemotherapy
Response to treatment	Failure (autologous bone marrow autograft)	Progression	Complete remission but relapse, 1 month later	Complete remission	Complete remission
Overall survival	144 months	4 months	21 months	127 months	280 months
Current status	Alive	Dead (Cytomegalovirus pulmonary infection)	Dead	Alive	Alive

[a]M: male; F: female; [b]LN: lymph node; [c]ALCL: anaplastic large cell lymphoma; [d]with a minor small cell component; [e]B symptoms: fever (i.e., temperature >38°C for 3 consecutive days); weight loss exceeding 10% of body weight for 6 months; drenching night sweats.

cally related to insect bites and were biopsied in three instances (# 2, 3 and 5). In one case (# 3) a skin biopsy of a tumor that developed at the site of a wasp bite led to the accurate diagnosis of "Ki-1 lymphoma" based on morphological features and reactivity of neoplastic cells with antibodies against CD30, EMA and CD3. ALK staining revealed areas consisting of large cells associated with a dominant population of small- to medium-sized cells suggesting an ALK-positive ALCL with a "composite pattern" (Figure 3 A-B). Case # 2 received insect bites of unknown nature on the wrist in March 1986. A skin biopsy was performed and a conventional examination revealed a dense lymphoid infiltrate rich in histiocytes (Figure 3C) initially considered to be a "non-specific reactive infiltrate". The patient was treated with antibiotics but the skin lesion persisted and 3 months later, she developed axillary lymphadenopathy that was resected. Immunostaining of the skin biopsy showed scattered medium- to large-sized cells, highlighted by CD30 and ALK stains, on a lymphohistiocytic background (Figure 3D). The lymph node was massively involved by an ALK-positive ALCL, lymphohistiocytic pattern. In case # 5, the first skin biopsy was also interpreted as a "reactive infiltrate" possibly related to insect bite. Given that no paraffin block was available, the H&E-stained section was used to perform ALK staining and revealed scattered, strongly positive cells of small to medium size on a dominant background of negative lymphoid cells admixed with histiocytes and plasma cells (Figure 1B). A second skin biopsy at the same site and surgical resection of enlarged axillary lymph node was performed 10 months later. Both were massively involved by a monomorphic infiltrate of large cells, many with "hallmark cell" features, strongly positive for ALK protein. A minor population of ALK-positive small cells was also observed suggesting an ALCL with a "common pattern" associated with a minor small cell component. Overall, the final diagnosis in these five cases was ALK-positive ALCL, with a "lymphohistiocytic pattern" in three cases (# 1, 2, and 4) and a "composite pattern" (common plus small cell pattern) in the other two cases (# 3 and 5). In all cases neoplastic cells were strongly positive for ALK and the staining pattern (i.e. cytoplasmic, nuclear and nucleolar

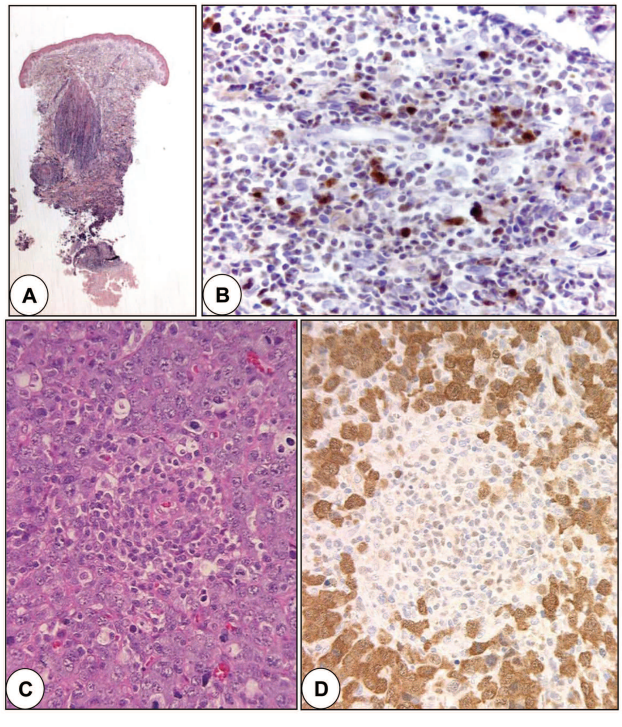

Figure 1. Morphological characteristics of skin and lymph node lesions of case n. 5: (A) (H&E stain, Leika DMD108 magnification x25) Initial skin biopsy of persistent lesion after insect bites: diffuse dense dermal and hypodermal infiltrate initially diagnosed as *non-specific reactive infiltrate*. (B) (ALK1, Leika DMD108, magnification x400) ALK1 staining performed on de-stained H&E section reveals scattered strongly positive cells of small to medium size in a predominant background of negative lymphoid cells admixed with histiocytes and plasma cells. (C) (H&E stain, Leika DMD108, magnification x400) Lymph node resected 1 year later massively involved by ALCL, common pattern with a minor small cell component (composite pattern) around vessels; (D) (same area) (ALK1, Leika DMD108, magnification x400). Large cells show cytoplasmic, nuclear and nucleolar ALK staining. Small cells positive for ALK exhibit a restricted nuclear staining.

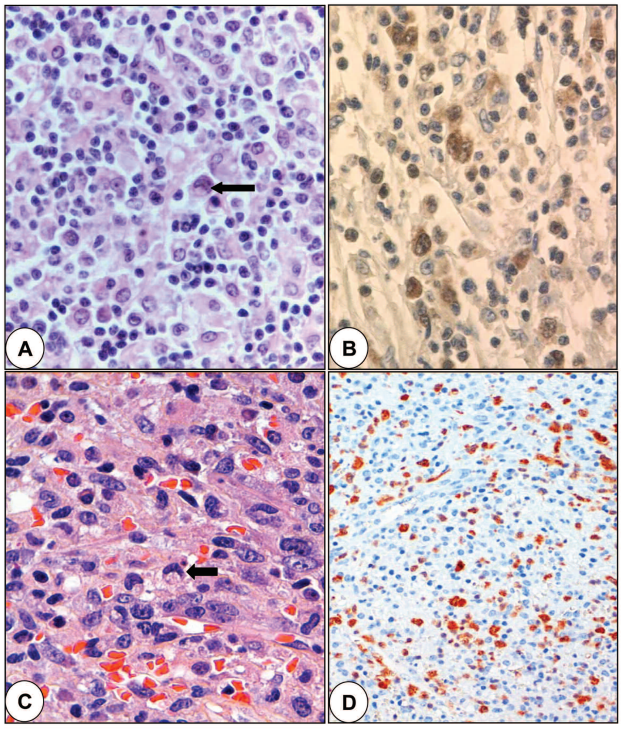

Figure 2. (A) (H&E stain, Leika DMD108, magnification x400). Case # 1, the normal lymph node architecture is effaced by a diffuse proliferation containing numerous histiocytes and scarce large cells with hallmark feature (arrow) characteristic of ALK-positive lymphohistiocytic ALCL. (B) (ALK1, Leika DMD108, magnification x630) ALK1 staining performed later shows some large atypical cells with cytoplasmic, nuclear and nucleolar ALK staining suggesting NPM-ALK protein expression. (C) (H&E stain, Leika DMD108, magnification x400) Morphological appearance of a lymph node biopsy of case # 4 initially considered a *hyperimmune reaction* and finally diagnosed as lymphohistiocytic ALCL with hallmark cells (arrow). (D) (ALK1, Leika DMD108, magnification x200) ALK1 staining showing scattered large malignant cells and some small cells with nuclear-restricted staining.

staining) was highly indicative of NPM-ALK fusion protein and the associated t(2;5) translocation.

All patients were eventually treated with multi-agent chemotherapy, associated with radiotherapy and autologous bone marrow transplant in one case (# 1). Three patients (cases # 1, 4, 5) achieved a complete remission and were alive without any evidence of disease at the last follow-up. Two patients died, one of a Cytomegalovirus-associated pneumonia during an aplastic phase following treatment (case # 2) and the other (case # 3) of disseminated disease 19 months after diagnosis.

Discussion

The cases reported here raise the question of whether the insect bites were coincidental or played a role in the development of these ALCL. Although we cannot exclude a coincidental association, the clinical context and the sequence of events between the insect bites, and the occurrence of both skin lesions and lymphadenopathy in the corresponding anatomical areas suggest a direct relationship. In addition to a report by Piccaluga *et al.*,[10] similar cases can be found in the literature even though the authors did not stress the potential role of insect bites in the clinical presentation or evolution of ALCL. Four of the six cases described by Kadin *et al.*[9] had a clinical diagnosis of insect bite and in two cases the initial differential diagnoses of pathologists included "non-malignant inflammatory disease". It is not, however, clear from their report whether the ALCL skin lesions followed or had been mistaken for arthropod bites.[9] Nevertheless, as in our cases, this study underscores the fact that some skin involvement in ALK-positive ALCL may closely resemble non-specific inflammatory infiltrate, as in cases # 2 and 5 of the present study, and that an accurate diagnosis cannot be made without ALK staining which may reveal scarce positive neoplastic cells. ALK staining may also be of crucial diagnostic value in the recognition of some variants of ALCL involving lymph nodes, particularly the lymphohistiocytic subtype.[12] It is noteworthy that the latter ALCL pattern, which is relatively rare (<10% of ALCL), was observed in three (# 1, 2, and 4) of the five cases. All these diagnostic uncertainties were responsible for the correct treatment being delayed for weeks to months.

Two other reports mention an insect bite in the clinical history of patients with ALCL. In 2000, Gould *et al.*[13] reported the case of a 4-year old girl presenting with a primary cutaneous ALK-positive ALCL that first appeared 6 months earlier coincidental to multiple urticarial arthropod bite reactions. Although, clinical details are missing, this case has some similarities with case n. 5 of the present study. The evolution was, however, different from the latter case since surgical resection was performed, no extra-cutaneous disease was found and the patient has been free of disease for more than 44 months since the surgical resection. The final diagnosis was solitary primary cutaneous ALK-positive ALCL. The other case was reported in 2007 by Rannan-Eliya *et al.*[14] A 14-year old female received an insect bite near her umbilicus. Six months later she presented with a fluctuant lesion in the same region and excision and drainage revealed granulation tissue without apparent evidence of malignancy. Subsequent biopsy of persistent skin induration revealed an ALK-positive ALCL with further dissemination and fatal relapse in the central nervous system.

In all these cases the nature of the arthropod bite was not clearly demonstrated except for the patient reported by Piccaluga *et al.*[10] who received a tick bite 20 days prior to the diagnosis of ALK-positive systemic ALCL. Serological tests revealed weak positivity for anti-rickettsial antibodies. A tick bite was also suspected in case # 1 of the present study, who developed a persistent skin lesion and lymphadenopathy, but no serological tests were performed. In the literature and in our cases the time elapsed between the insect bite and the diagnosis of ALCL varied from a few weeks to 6 months.

Ticks carry many pathogens, the most common being *Borrelia burgdorferi*, the spirochete responsible for Lyme disease which has been implicated in the pathogenesis of at least a subset of cutaneous marginal-zone B-cell lymphomas[15-17] and one case of angioimmunoblastic T-cell lymphoma.[18] Several reports have been published on the puzzling relationship between insect bites and lym-

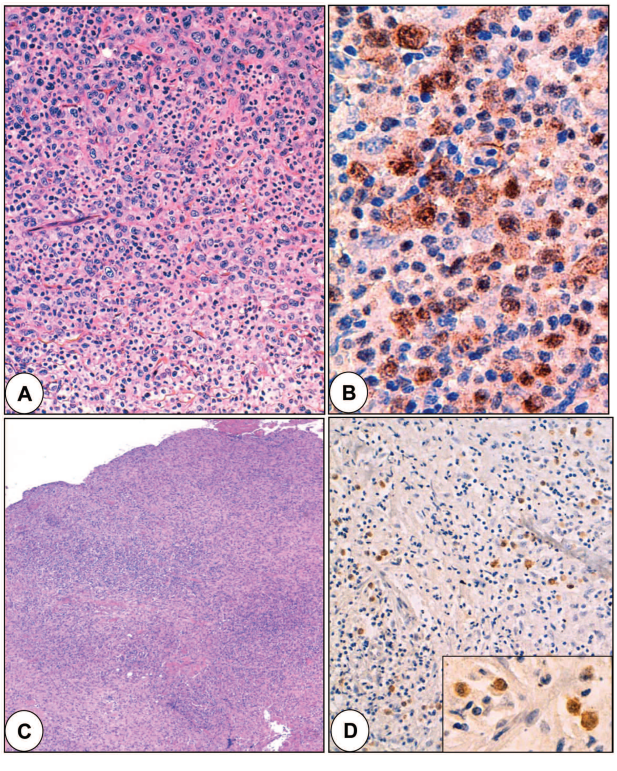

Figure 3. (A) (H&E stain, Leika DMD108, magnification x200). Case # 3, skin biopsy of the tumor that developed at the site of a wasp bite shows massive dermal involvement by sheets of large malignant cells, associated with atypical small cells, which led to the diagnosis of *Ki-1 lymphoma* on the basis of CD30, EMA and CD3 expression. (B) (ALK1, Leika DMD108, magnification x400) ALK staining reveals strong cytoplasmic, nuclear and nucleolar reactivity of large cells associated with a predominant population of small to medium sized cells suggesting an ALK-positive ALCL *composite pattern*. (C) (H&E stain, Leika DMD108, magnification x25). Case # 2, General aspect of the skin biopsy of the wrist lesion at the site of an insect bite. (D) (ALK1, Leika DMD108, magnification x25) ALK staining shows scattered large to medium-sized cells on a lymphohistiocytic background. Insert: ALK staining pattern highly indicative of NPM-ALK protein expression (magnification x400).

phoma. In 1965, Weed *et al.* described the occurrence of unusual cutaneous lesions secondary to insect bites in certain patients with chronic lymphocytic leukemia.[19] These lesions were attributed to an exaggerated immune response to mosquito antigens, perhaps due to a greater local mobilization of lymphocytes in these patients. This same phenomenon was subsequently reported not only in patients with chronic lymphocytic leukemia, but also in patients with other lymphoproliferative diseases.[20] However, as only few patients recalled arthropod assaults, the role of insect bites in the initiation of such eruptions has remained controversial and the term "insect bite-like reaction" has been proposed.[20]

Another example of the role of insect bites in lymphoproliferative disorders is the syndrome of hypersensitivity to insect bites associated with chronic active Epstein-Barr virus infection.[21-23] In this syndrome, $CD4^+$ T cells stimulated by mosquito antigens may reactivate latent Epstein-Barr virus infection in NK/T cells and contribute to their unregulated expansion within inflammatory skin lesions and in the peripheral circulation.[24-28] A significant proportion of these patients die of Epstein-Barr virus-positive NK/T-cell lymphoma or hemophagocytic syndrome.[21-23,29]

A comparable scenario can be proposed regarding the possible role of insect bites as a triggering factor in the presentation of ALCL. Insect bite-associated antigens could result in an influx of $CD4^+$ T lymphocytes, some of them bearing the t(2;5) translocation. The presence of the *NPM-ALK* fusion transcript has been detected by real-time reverse transcriptase polymerase chain reaction analysis in reactive lymph nodes[30] and normal peripheral blood samples of healthy individuals.[31] The subsequent release of cytokines at the site of an insect bite could act as a 'second hit', eliciting the activation and proliferation of the latter cells, which would then express the oncogenic NPM-ALK fusion protein and undergo uncontrolled proliferation. Alternatively, children might have occult disease at the time of the bite, with the release of cytokines precipitating an influx of neoplastic cells to the site of inflammation via chemotaxis.

Authorship and Disclosures

GD, SP, and EJ recruited the patients. LL, GD and EJ wrote the paper.

The authors reported no potential conflicts of interest.

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