

Case report

Cutaneous Richter Syndrome mimicking a lower limb cellulitis infection - a case report and review of the literature.

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Abstract

Richter syndrome (RS) is characterized by the development of a high-grade lymphoma in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Herein, we present the case of an 85-year-old woman with a 3-year history of stable asymptomatic CLL that developed a cutaneous RS. The patient presented with painless inflammation in the left leg and foot that was initially diagnosed as a cellulitis infection. She was treated accordingly with ceftriaxone and clindamycin. However, after completing the antibiotic regimen, not only did the inflammation persist, but also superimposed painless nodules gradually appeared on the left leg and foot over the course of four months. The histopathological examination of the nodules revealed a large B-cell cutaneous lymphoma. The patient underwent chemotherapy with CVP, followed by R-CHOP, resulting in a reduction of size of the nodules and remission of the inflammation. The patient died five months after the diagnosis owing to a bacterial pneumonia. We identified in previous reports a total of fifteen cases of cutaneous RS. Most cases presented with rapidly growing tumors or multiple erythematous nodules, similar to our case. This case of a cutaneous RS mimicking a cellulitis infection underlines the importance of a low threshold for performing biopsies of suspicious skin lesions in patients with CLL/SLL.

Keywords: Leukemia, Lymphocytic, Chronic, B-Cell; Lymphoma, B-Cell; Skin Neoplasms

Introduction

Richter syndrome (RS) is characterized by the development of a high-grade non-Hodgkin or Hodgkin lymphoma in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). A recent review has found a large variation between historical series regarding the prevalence of RS in CLL patients ranging from 1% to 11% [1–7]. Most frequently RS involves the lymph nodes or bone marrow nevertheless, different extranodal presentations have been observed in patients with CLL [8].

Herein, we present a case of RS in which nonspecific skin lesions were the presenting manifestation, and where the skin biopsy was fundamental to the correct diagnosis.

Case report

An 85-year-old woman with a 3-year history of stable asymptomatic CLL presented with painless inflammation in the left leg and foot in association with mild asthenia. The condition was initially diagnosed as a cellulitis infection and treated accordingly with a combined intravenous antibiotic regimen of ceftriaxone and clindamycin. After completing the treatment the inflammatory signs persisted despite that fact that the laboratory tests showed no elevation of inflammatory parameters, such as C-reactive protein and erythrocyte sedimentation rate. The hypotheses of severe stasis dermatitis and lipodermatosclerosis were then considered but the application of topical corticosteroids and compression measures were also unsuccessful. After four months she was referred to our outpatient department not only because the inflammation persisted, but also because superimposed painless nodules had gradually developed on the left leg and foot.

Upon examination, the left leg and foot exhibited a bright red erythema and edema. In addition, three cutaneous nodules, hard and painless upon palpation and displaying a red-purple hue were identified: two located on the anterior surface of the left leg and another one on the dorsum of the left foot (Figure 1). The remaining physical examination was unremarkable, including the absence of any palpable lymph nodes or hepatosplenomegaly.

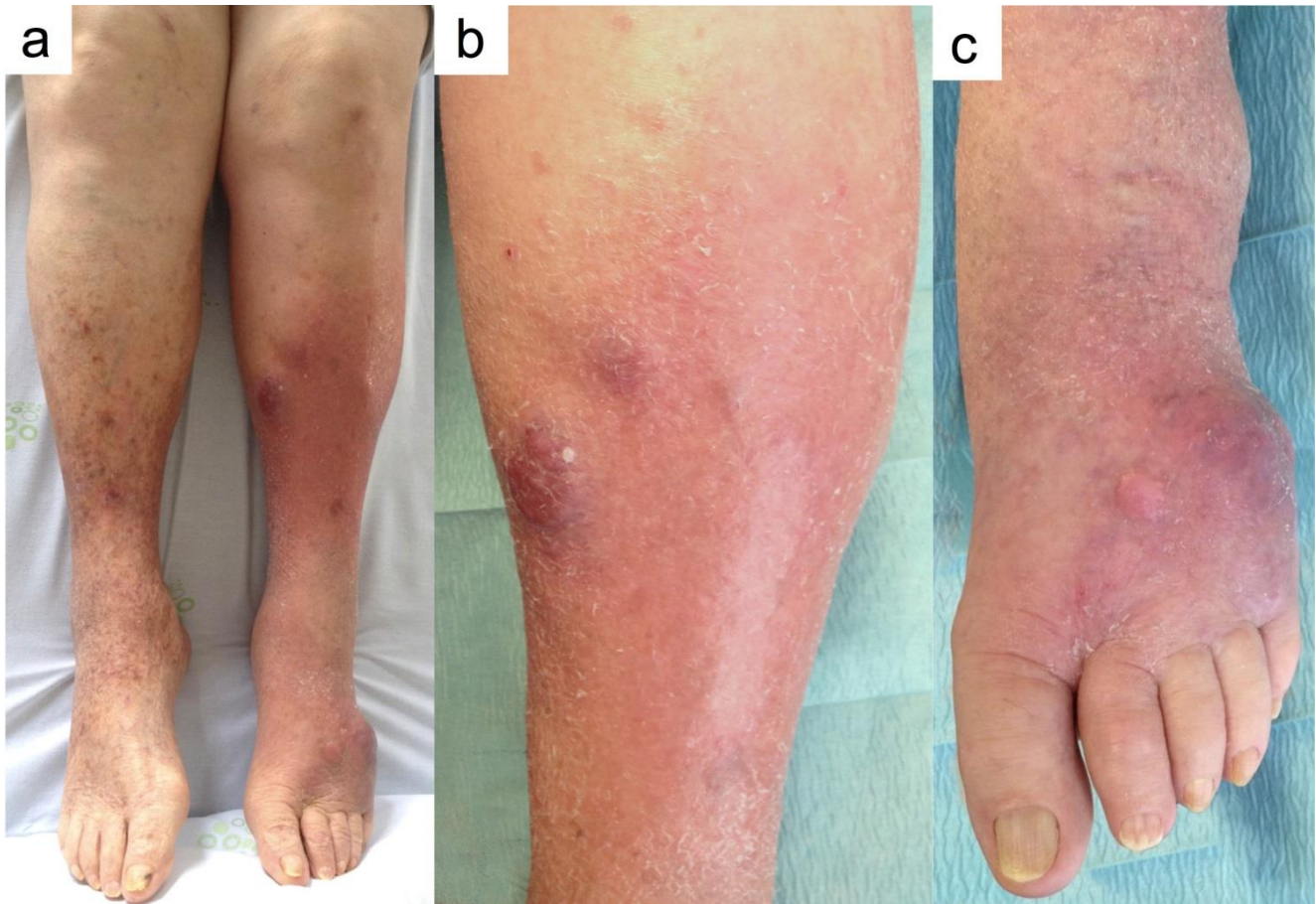


Figure 1. (a) Erythematous nodules on the left leg and foot. (b) and (c) close-up views of the two biopsied nodules

An incisional biopsy of two nodules was performed (Figures 1b and 1c), and in both cases the histopathological examination revealed a dense monomorphic infiltrate of large cells (Figure 2a) without epidermotropism (Figure 2b). The neoplastic cells exhibited regular nuclei with prominent nucleoli and a high mitotic index in the dermis and subcutis (Figure 2c). The majority of the infiltrating cells were CD45+ and CD20+ B cells. Altogether, these findings supported the diagnosis of a diffuse large B-cell cutaneous lymphoma (DLBCL).

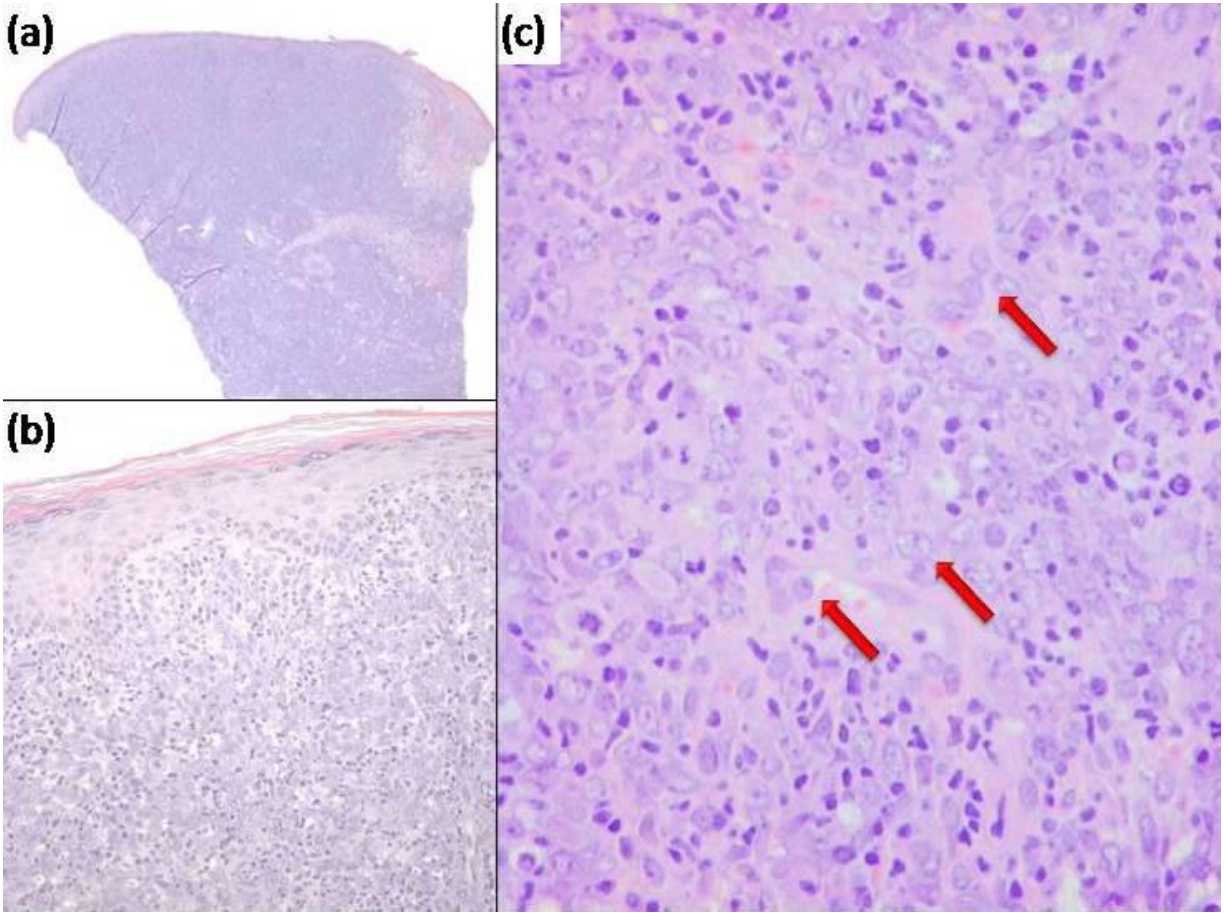


Figure 2. Skin specimen biopsy of the leg nodule. (a) Extensive and diffuse infiltration of the skin with mononuclear cell population (HE, x40). (b) Tumor cells without evidence of epidermotropism (HE, x100). (c) Neoplasia composed by large cells with regular nuclei with prominent nucleoli (red arrow) and a high mitotic index (HE, x200).

The patient's laboratory tests showed normal red blood cell and platelet counts. The white blood cell count was $11.20 \times 10^9/L$ (normal range: $4.0 - 11.0 \times 10^9/L$) with 44.5% of lymphocytes. In addition, peripheral blood immunophenotyping identified a monoclonal B-lymphocyte population expressing surface IgG λ , CD5, CD20, CD23, CD43 and CD79b, confirming the previously diagnosed B-cell CLL. Bone marrow aspirate and biopsy were normal and other biochemistry and serological assessments were also normal or negative, including $\beta 2$ -microglobulin level, lactate dehydrogenase activity (LDH), and tests for human immunodeficiency virus and hepatitis. Likewise, chest and abdominal computed tomographies (CT) revealed no lymphadenopathy or hepatosplenomegaly.

Facing a DLBCL developing in the setting of a CLL (stage 0 or A, according to the classification of Rai or Binet respectively), the diagnosis of cutaneous RS was made. The patient was treated with the chemotherapy association CVP (cyclophosphamide, vincristine and prednisolone), followed by two courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). After four months of treatment, a significant improvement of the cutaneous lymphoma was observed (Figure 3), but the patient died one month later owing to a bacterial pneumonia.



Figure 3. Skin lesions of the left leg (a) and ipsilateral foot (b), after four months of chemotherapy.

Discussion and conclusion

Even though CLL is classified as a low-grade lymphoproliferative disorder it can progress to more aggressive forms of lymphoma at a estimated rate of 0.5-1.0% per year [2–4,9–11]. The classical presentation of RS is with primary lymph node involvement however, RS can involve primarily extranodal localizations such as the gastrointestinal tract, liver, tonsils, bone marrow and more rarely the skin [12], as it was the case of our patient. In contrast to primary cutaneous lymphomas, the majority of which are T-cell lymphomas, most reported cases of RS are of B-cell type, particularly the DLBCL [13]. Furthermore, according to the Hans-Choi algorithm (based on immunohistochemistry), 90% to 95% of DLBCL transformations in patients with CLL are of the more aggressive activated B-cell subtype [11,14].

Advanced Rai stage (III-IV) at CLL diagnosis and lymph nodes >3cm on physical examination are associated with higher risk of future RS [2,10,15]. In addition, different reports have shown that different germline genetic polymorphisms (in B-cell lymphoma 2, CD38 and low-density lipoprotein receptor-related protein 4), certain characteristics of the B-cell receptor (IGHV mutations), genetic abnormalities (del(11q23.1), del(17p13.1), del(15q21.3), add(2p25.3), inactivation of p53, inactivation of CDKN2A, C-MYC activation, trisomy 12, NOTCH1 mutations), and several other biologic characteristics of the leukemic B cells (such as shorter telomere length) are associated with RS [7]. However, their precise role and functional consequences in the pathogenesis of RS remain to be elucidated. The relation between CLL therapies and subsequent development of RS is also unclear as is the case of infectious agents such as Epstein-Barr virus [7].

Although nonspecific, several clinical signs and symptoms should raise the suspicion of RS in patients with CLL. These include high-grade fevers, rapidly enlarging lymph nodes, weight loss, hypercalcemia, and a markedly elevated LDH [7]. Some of our patient's clinical characteristics were similar to those of the other fifteen cases of cutaneous RS previously documented in the literature (Table 1).

Article	Skin presentation	Gender and age	Time between CLL and RS	Extra-cutaneous involvement	Prognosis/survival after RS diagnosis
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				diagnosis		
Yu, 2012 [18]	Face and ears	2-3 mm red-blue papules	♀ 77 years	3 years	None	8 years of follow-up
	Back	Erythematous rash	♂ 63 years	7 years	Adenopathy	Death after 5 years of follow-up.
	Chest	Erythematous plaques and nodules	♂ 61 years	7 years	Adenopathy, splenomegaly	Death after 20 days of follow-up
Duong, 2010 [16]	Forearm	2 large purple nodules	♀ 62 years	8 months	Adenopathy, splenomegaly	Complete resolution of cutaneous lymphoma. Death after 5 years of follow-up (cerebral lymphoma)
	Forearm, Shoulder, Feet, Thighs	Nodules	♂ 53 years	18 months	None	Death after 10 years of follow-up
	Nose, forearm, chest	Nodules with central necrosis	♂ 55 years	6 years	Adenopathy	Death after 2 years of follow-up
	Forearm, trunk	Nodules and erythematous plaque	♂ 59 years	4 years	Adenopathy	Complete resolution of skin lymphoma. 4 years of follow-up
Yamazaki, 2009 [12]	Back	Flesh-colored papule	♂ 76 years	5 years	None	Complete resolution of skin lymphoma. 4 years of follow-up
Robak, 2005 [1]	Nose	Rapidly enlarging tumor on the nose	♀ 77 A	7 months	Splenomegaly	Complete resolution of cutaneous lymphoma
Ratnavel, 1999 [17]	Abdomen	Erythematous nodule	♀ 66 years	8 years	None	Complete resolution of cutaneous lymphoma after surgery. 3-year of follow-up
	Legs and upper trunk	Ulcerated nodules	♂ 78 years	Simultaneous	Adenopathy, hepatosplenomegaly	Death after 4 months of follow-up
Zarco, 1993 [23]	Limbs	Erythematous nodules	♂ 45 years	5 years.	Adenopathy, hepatosplenomegaly	Death after 2 years of follow-up
Novice, 1989 [24]	Lower lip	Hyperkeratotic dome-shaped nodule with central invagination	♂ 74 years	Simultaneous.	Adenopathy, splenomegaly	Refused treatment after 2 months
Trump, 1980 [19]	Scalp	Nodules	NA	NA	Splenomegaly	Death after 7 months of follow-up

Table 1. Reported cases of cutaneous Richter syndrome

More specifically, most cases presented with rapidly growing tumors or multiple erythematous nodules at various body sites. In those reports, the mean age at the diagnosis of RS was 65 years and the mean interval between the initial CLL diagnosis and the cutaneous RS diagnosis was 45 months. On the other hand, the majority of the cases exhibited some form of systemic involvement (i.e. bone marrow, lymph nodes, or viscera), a feature not observed in our patient.

In contrast to RS with nodal presentation, where an excisional biopsy is the gold-standard for the diagnosis, in cutaneous RS the histopathological examination of an incisional biopsy is often successful in establishing the diagnosis. In other extranodal presentations the selection of the tissue for biopsy can be assisted by PET/CT [7]. Once the diagnosis of RS has been confirmed, bone marrow aspirate and biopsy should be performed to complete staging. FISH studies on either peripheral blood or marrow tissue should also be undertaken to identify acquisition of del(17p13.1), because this genetic finding has therapeutic and prognostic implications (usually associated with rapid disease progression, poor response to therapy, early relapse, and short survival) [7].

In most cases RS is associated with an ominous outcome, with a mean survival period of 8 months despite chemotherapy [4]. The most important determinant of the clinical outcome in patients with RS is the clonal relationship of the DLBCL to the underlying CLL [7]. The median survival of patients with clonally related RS (corresponding to approximately 80% of cases) is shorter, ranging from 8 to 14 months [7]. Having a DLBCL clonally unrelated to CLL (corresponding to approximately 20% of cases) portends a more favorable prognosis, with a median survival of approximately 62 months [11]. In many centers, including our own, the techniques to determine clonal relationship between CLL and DLBCL are not routinely available. In these instances prognostic factors such as the patient's performance status, serum LDH, platelet count, tumor size, presence of TP53 disruption, number of prior therapies and response to induction therapy, can be used to predict the clinical outcomes in patients with CLL and RS [4,11]. In this regard, some authors have also observed a better prognosis for cutaneous RS compared to other variants [1,12,16–19]. Even though our patient was free of systemic involvement, which could portend a better prognosis, unfortunately she did not overcome a bacterial lung infection.

There are no randomized control trials to guide therapy for RS patients. Based on treatments regimens used for other B-cell non-Hodgkin lymphomas, anthracycline-based therapy such as CHOP and R-CHOP have been the initial standard treatment for CLL patients who experience RS [20,21]. Other trials have evaluated different regimens such as hyperCVXD (fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone) [22] and OFAR (oxaliplatin, fludarabine, cytarabine and rituximab) [16]. In spite of the fact that the complete response and/or overall response rate in some of these trials was superior to those obtained with R-CHOP, the median survival was significantly lower. Based on experience with intense combination chemotherapy-based regimens Parikh et al have proposed a treatment algorithm for RS [7]. They propose to treat the 20% of patients with clonally unrelated DLBCL with R-CHOP (similar to patients with de novo DLBCL). For those patients who do not achieve a complete response, salvage therapy with RICE (rituximab, ifosfamide and etoposide) or with RDHAP (rituximab, dexamethasone, cytarabine and cisplatin), followed by an autologous stem cell transplantation should be considered. For the 80% patients with clonally related DLBCL, their first choice of therapy is a clinical trial given the suboptimal efficacy of the standard treatment approaches. If a clinical trial is not available, R-CHOP is considered as the initial treatment followed by consolidation with stem cell transplantation. This algorithm also advocates that if a patient has received prior anthracycline therapy, platinum-based induction regimens such as OFAR, RDHAP, or RICE may be considered. Allogenic stem cell transplantation is the preferred approach for patients with clonally related DLBCL.

Our report emphasizes the need for awareness and the importance of an early detection of cutaneous lymphomas. This concern is even more significant in patients suffering from CLL, which tend to have worse prognosis than those with similar primary cutaneous lymphomas. Even though the cutaneous presentations can be associated with a more favorable prognosis, RS is associated with a very rapid disease progression, limited therapeutic options, and a poor survival. In this regard an incisional biopsy is mandatory for all suspicious cutaneous lesions in patients with CLL since the early detection of RS and prompt institution of therapy offers the best chance for remission. The discovery of biologic features of the B-cell that have prognostic and therapeutic implications prompt the need for a more widespread use of laboratory techniques such as the determination of the clonal relationship between the CLL and the DLBCL.

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