# Cutaneous Richter syndrome: Report of 3 cases from one institution

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***Background:*** Richter syndrome (RS) is large-cell transformation of chronic lymphocytic leukemia (CLL). It commonly involves lymph nodes and bone marrow, but may rarely manifest in skin. Certain triggering factors, such as Epstein-Barr virus infection and p53 overexpression, have been implicated in the pathogenesis of RS. Here, we present 3 cases of cutaneous RS from our institution with a follow-up period of up to 8 years.

***Objective:*** We present a series of cutaneous RS from a single institution with the longest follow-up period (up to 8 years) to date.

***Methods:*** Clinical characteristics were collected and histopathological findings of skin biopsy specimens were analyzed.

***Results:*** All 3 patients had prior CLL and later developed cutaneous RS lesions. The mean age at the diagnosis of cutaneous RS was 67 years old. The time intervals between CLL and cutaneous RS were 3 to 8 years. Skin biopsy specimens demonstrated dermal nodular or perivascular infiltrates of large B cells, showing similar immunophenotypes to the lesional cells in the original CLL. Overexpression of p53 and positive stain for Epstein-Barr virus–encoded small RNA was found in one patient. One patient remained alive 8 years after the diagnosis whereas the other two died of the disease at 5 years and 3 weeks, respectively, after the onset of cutaneous RS.

***Limitations:*** Three patients with RS were followed up for up to 8 years.

***Conclusions:*** Our findings suggested that, in contrast to extracutaneous RS, cutaneous RS generally has a less aggressive course with longer survival unless other worse prognostic factors are present. (J Am Acad Dermatol 2012;67:e187-93.)

***Key words:*** chronic lymphocytic leukemia; cutaneous Richter syndrome; prognosis.

The development of high-grade non-Hodgkin lymphoma in patients with chronic lymphocytic leukemia (CLL) is known as Richter syndrome (RS). The syndrome was first described in 1928 by Maurice N. Richter who reported a patient with rapidly generalized lymphadenopathy and hepatosplenomegaly associated with CLL.[1] Later on, more cases were documented and the condition was named as "histiocytic lymphoma" in association with CLL.[2] In 1964, Lortholary et al[3] described 4 similar cases and suggested the terminology of "Richter syndrome" to replace "histiocytic lymphoma." RS is estimated to occur in 3% to 10% of patients with CLL

*Abbreviations used:*

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|---|---|
| CLL: | chronic lymphocytic leukemia |
| EBER: | Epstein-Barr virus–encoded RNA |
| EBV: | Epstein-Barr virus |
| RS: | Richter syndrome |

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and occasionally develops de novo without a preexisting CLL.[2,4,5] RS is often characterized by an abrupt onset of fever, weight loss, night sweats, progressive lymphadenopathy, hepatosplenomegaly, and lactate dehydrogenase elevation.[2,6] RS usually develops in lymph nodes or bone marrow, although it may occur at other extranodal sites, including gastrointestinal tract, eye, testis, central nervous system, nasopharynx, kidney, and skin.[5] Skin involvement of RS is rare with only a handful of cases reported in the literature.[2,6-14] RS presenting as a skin lesion with the initial diagnosis made by skin biopsy specimen is quite rare. Histopathological examination of the affected organ shows an atypical lymphoid infiltrate composed of large cells with enlarged nuclei, prominent nucleoli, and abundant basophilic cytoplasm.[1] The large cells usually demonstrate similar immunophenotype as CLL and are positive for CD20, CD5, and CD43 with clonal IgH gene rearrangements. CD30 positivity may be seen.[9] The survival for RS is often poor.[6,15]

**CAPSULE SUMMARY**

- Richter syndrome (RS) is large-cell transformation of chronic lymphocytic leukemia.
- Skin involvement of RS is rare with only a handful of cases reported in the literature.
- We present 3 cases of cutaneous RS from our institution with a follow-up period of up to 8 years.
- The prognosis of cutaneous RS in our series was more favorable than that of extracutaneous RS.

The molecular events that underlie RS in patients with CLL are not yet well understood. Various hypotheses, such as karyotypic modifications,[16,17] mutations in tumor suppresser genes,[18-20] and viral infection,[21] have been proposed in the past, but none has been conclusively proven.

Herein, we report a series of 3 cases of cutaneous RS from a single institution. All patients had histories of CLL, and the diagnoses of RS were made on their skin biopsy specimens. We analyzed the clinical and histologic features of these patients during a follow-up period between 2 weeks and 8 years. We further explored the possible pathogenesis and prognostic indicators in these patients.

## METHODS

Between 2002 and 2008, 3 patients with CLL were given the diagnosis of cutaneous RS in our institution. The slides were examined by 4 pathologists (L. Y., D. R. F., L. D. S., and L. M.) to confirm the diagnoses. Immunohistochemistry of skin specimens, flow cytometry of bone marrow and peripheral blood, and cytogenetic study results were also reviewed.

Immunohistochemical stains for lymphoid markers, including CD5 (clone SP19, Cell Marque, Rocklin, CA), CD20 (clone L26, Ventana Medical Systems, Tucson, AZ), CD30 (clone BERH2, Dako, Carpinteria, CA), CD43 (clone MT1, Cell Marque), CD79a (clone JCB117, Dako), and mouse monoclonal anti-p53 antibody (clone DO-7, Ventana Medical Systems) were performed on formalin-fixed paraffin-embedded 5-$\mu$m tissue sections using the automated BenchMark immunohistochemistry staining system (Ventana Medical Systems) as previously described.[22] Tonsil tissue served as positive control for lymphoid markers while tissue from human endometrial cancer served as positive control for p53.

Epstein-Barr-virus (EBV)-encoded RNA (EBER) in situ hybridization was conducted on formalin-fixed paraffin-embedded 5-$\mu$m tissue sections using a primary rabbit antifluorescein antibody (prediluted, Ventana Medical Systems) followed by ISH iVIEW detection kit (Ventana Medical Systems).

## CASE REPORTS

### Case 1

A 74-year-old woman with a 10-year history of CLL/small lymphocytic lymphoma presented to our dermatology clinic in 1999 with a nodule on her nose, which was clinically diagnosed as rhinophyma and treated with doxycycline. Five months later, a skin biopsy specimen of this lesion was taken and showed a dense monotonous infiltrate of small lymphocytes in the dermis and subcutis. The majority of the infiltrating cells were $CD79a^+$ and $CD20^+$ B cells that coexpressed CD5 and CD43. A diagnosis of cutaneous CLL was made. The patient's white blood cell count was 19,500/$\mu$L (normal range: 4.1-10.9 $\times$ $10^3/\mu$L) at the time. The lesion gradually resolved after local radiation. In 2002, she developed multiple 2- to 3-mm red-blue papules on her face and on the pinnae of both ears. Skin biopsy specimens showed a dermal nodular infiltrate of large B cells expressing CD20, CD79a, CD43, and weak CD5. In the context of her history of CLL, cutaneous RS was diagnosed. Physical examination and computed tomography scans failed to reveal any lymphadenopathy or splenomegaly. Her white blood cell count was 18,500/$\mu$L with an absolute lymphocyte differential count of 13,900/$\mu$L (normal range: 1.2-4.0 $\times$ $10^3/\mu$L).