Secondary skin involvement in gastric diffuse large B-cell lymphoma treated with chidamide
A case report
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Abstract
Rationale: Diffuse large B-cell lymphoma (DLBCL) is a neoplasm of large B lymphoid cells that exhibits diffuse growth patterns. Patients may present with nodal and/or extranodal disease. The most common extranodal site is the gastrointestinal tract, while skin is less common.

Patient concerns: We report a case of secondary skin involvement of an original gastric DLBCL, which has achieved a complete response after treatment with chidamide.

Diagnoses: Initially, the diagnosis of gastric DLBCL is clear, and this patient responded well to systemic chemotherapy (rituximab + cyclophosphamide + epirubicin + vincristine + prednisone) after 8 cycles. Thirty months later, some rapidly enlarging skin nodules on his arm were found. These skin nodules were diagnosed as secondary cutaneous DLBCL based on the clinical features, positron emission tomography-computed tomography, and histomorphologic and immunohistochemical expression.

Interventions: Steroids, interferon-α, and radiation had little therapeutic effect. We treated the patient with chidamide at 30 mg twice per week in combination with dexamethasone.

Outcomes: The skin nodules regressed 3 weeks later. During the 1-year follow-up period, the patient is still in treatment with chidamide without adverse reactions.

Lessons: To the best of our knowledge, this is the first case of secondary skin DLBCL reported to exhibit a complete response to chidamide, which provides a novel therapeutic strategy for secondary skin DLBCL. However, more cases are still needed to further validate its efficacy.

Abbreviations: BM = bone marrow, CBCL = cutaneous B-cell lymphoma, CR = complete remission, DLBCL = diffuse large B-cell lymphoma, FDG PET-CT = F-fluorodeoxyglucose positron emission tomography-computed tomography, HDACis = histone deacetylase inhibitors, IHC = immunohistochemical, NHL = non-Hodgkin lymphoma, PCDLBCL-LT = primary cutaneous DLBCL and leg-type lymphoma, PCMZL = primary cutaneous marginal zone B-cell lymphoma, PR = partial response, PTCL = peripheral T-cell lymphoma, R-CHOP = rituximab + cyclophosphamide + epirubicin + vincristine + prednisone.

Keywords: chidamide, diffuse large B-cell lymphoma, secondary skin involvement

1. Introduction
Diffuse large B-cell lymphoma (DLBCL) constitutes 25% to 30% of adult non-Hodgkin lymphomas (NHLs) in Western countries and a higher percentage in developing countries. DLBCL is more common in the elderly and is slightly more common in males than in females. Patients may present with nodal and/or extranodal disease, and in up to 40% of cases, the disease is at least initially confined to extranodal sites. The most common primary extranodal sites of DLBCL are the gastrointestinal tract, the head and neck, and the skin/skin/soft tissue. In a large cohort with DLBCL, primary skin/soft tissue involvement accounted for 3.3% of all cases. Depending on the site of involvement, DLBCL with cutaneous involvement can be divided into 2 distinct subsets: primary cutaneous DLBCL, which initially presents on the skin; and DLBCL accompanied by secondary spread to the skin. Secondary cutaneous DLBCL is more commonly associated with an advanced stage and a higher international prognostic index than primary cutaneous DLBCL. The multiplicity of skin nodules and the time point of cutaneous involvement are associated with the prognosis of secondary cutaneous DLBCL.

With the aims of providing useful information in similar cases, we report a case of a DLBCL with secondary skin involvement. The patient exhibited an excellent response to chidamide. Chidamide may have a novel role in management of this aggressive secondary cutaneous DLBCL.

2. Case report
A 49-year-old male presented with epigastric aching, heartburn, and intermittent tarry stool without fever, night sweats, and
weight loss in October 2009. He was admitted to our hospital in November 2009 and examined with a gastroscope. A $3 \times 5$ cm ulcer with purulent secretion was found at the bottom of the stomach (Fig. 1A). Gastroscopic biopsies and immunohistochemical (IHC) staining showed positive CD20, CD79a, Pax-5, Mum1, Bcl-2, Bcl-6 expression, and negative CD5, CD10, EMA expression. There was a high proliferative index (Ki-67+++; Fig. 1B–E). Neither a bone marrow (BM) smear nor a BM biopsy showed evidence of BM involvement. The patient was diagnosed with primary gastric DLBCL. He was treated with an R-CHOP (rituximab 375 mg/m$^2$ d1, cyclophosphamide 750 mg/m$^2$ d2, epirubicin 80 mg/m$^2$ d2, vincristine 2 mg d2, and prednisone 100 mg d2–6) regimen and achieved complete remission (CR) after 4 cycles. We continued treatment with 4 cycles of R-CHOP to consolidate therapy and followed up every 3 months.

However, the patient found a subcutaneous $2 \times 3$ cm nodule, without pain, itching, redness, swelling, or bursting, on the inside of his right upper arm 30 months later. Topical skin steroids
therapy produced poor effect. Moreover, the subcutaneous nodule enlarged quickly. During a year and a half, the subcutaneous nodules became more and more in arms, legs, and buttocks. A skin biopsy from his right lower limb was collected on July 29, 2014. IHC of the skin biopsy revealed positive CD79a, CD20, BOB.1, LM02, Bcl-2, EZH2, Pax-5, and MUM1 expression, but negative for CD10 and Bcl-6 (Fig. 2). There is no evidence to reveal the disease elsewhere, except the skin. Based on these results and the history of gastric DLBCL, a diagnosis of secondary skin DLBCL was made. There were no abnormal changes on a follow-up 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) scan on August 11, 2014. The patient was given interferon-α treatment, and some of the skin nodules disappeared. However, new nodules always appeared later. The biggest nodule was resected and treated with radiation therapy. One year later, the patient could not tolerate the side effects of the interferon-α and stopped treatment. A new biopsy of a nodule on his left lower limb was performed in September 2015, and the same IHC results were obtained. A PET-CT scan performed on October 26, 2015 again, revealed a slight uptake of FDG in the skin of his left limb (Fig. 3A). A skin biopsy of the left lower limb was collected for the third time on July 4, 2017, and we obtained the same IHC results (Fig. 3B–E). Henceforth, the patient was diagnosed with relapsed/refractory DLBCL with only skin involvement.

Follow-up gastroscopies every 3 months showed nothing during this period. Chidamide at 30mg twice per week in combination with dexamethasone at 15 mg q.d. for 5 days per month was initiated on August 4, 2017, and resulted in rapid improvement and CR after 3 weeks (Fig. 4). The patient is on treatment with chidamide presently, and the duration of follow-up is a year up to now. The patient remains in CR without adverse reactions at the time of this writing.

3. Discussion
DLBCL can be cured with chemotherapy. The CHOP regimen has been the mainstay therapy for several decades. The addition of the anti-CD20 monoclonal antibody (rituximab) to CHOP (named as R-CHOP) has led to a marked improvement in survival.[6] The patient in this report responded well to R-CHOP and achieved CR after 4 cycles. Then another 4 cycles of R-CHOP were used to consolidate the therapy. Every 3 months follow-up proved that the primary disease has been well-controlled.

Primary cutaneous lymphoma encompasses a unique, heterogeneous group of lymphoproliferative disorders that have a primary cutaneous manifestation in the absence of systemic involvement of the lymph nodes, BM, or visceral organs at the time of diagnosis. The primary cutaneous lymphomas are less

Figure 2. Immunohistochemical analysis of skin biopsy (July 29, 2014). (A) Skin biopsy revealed diffuse infiltration by large lymphoid cells in the dermis and subcutaneous tissue (hematoxylin–eosin, ×200). (B) CD20 (×200). (C) BCL-2 (×200). (D) Ki-67 (×200).
aggressive and have a better overall prognosis.\textsuperscript{5,7} The absence of evident extracutaneous disease is a necessary condition for diagnosis of primary cutaneous B-cell lymphoma (CBCL).\textsuperscript{10} The patient in this report had a history of gastric DLBCL, the question is that the cutaneous lymphoma was primary or secondary.

Primary CBCL comprises a variety of lymphoproliferative disorders characterized by clonal proliferation of B cells and primarily involves the skin. The WHO-EORTC classification sorts CBCL into 4 distinct types as follows: primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicular centre lymphoma, primary cutaneous DLBCL and leg-type lymphoma (PCDLBCL-LT), and PCDLBCL-other.\textsuperscript{10} PCDLBCL-LT is characterized by skin lesions that mainly occur on the legs and predominantly contain diffuse sheets of centroblasts and immunoblasts, which spare the epidermis but frequently extend deep into the dermis and subcutaneous tissue.\textsuperscript{10} PCDLBCL-LT commonly

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\textbf{Figure 3.} F-18 fluorodeoxyglucose (FDG) PET-CT and immunohistochemical analysis of skin biopsy (July 4, 2017). (A) A PET-CT scan revealed a slight uptake of FDG in the skin of his left limb (black and white arrow). (B) Skin biopsy revealed diffuse infiltration by large lymphoid cells in the dermis and subcutaneous tissue (HE, \texttimes200). (C) CD20 (\texttimes200). (D) BCL-2 (\texttimes200). (E) Ki-67 (\texttimes200). PET-CT = positron emission tomography-computed tomography.
\end{center}
affects elderly females and presents with rapidly progressive tumors. Approximately 10% of cases may involve cutaneous sites other than the lower legs, and extracutaneous dissemination is common. Patients present with solitary or multiple, rapidly growing, red to bluish-red firm tumors on one or both legs. In 10% to 15% of cases, the lesions are localized to other sites, such as the trunk, head-neck, and upper arms. PCDLBCL-LT nearly always exhibits strong Bcl-2, IRF4/MUM1, and Foxp1 expression. Bcl-6 is expressed in most cases, whereas CD10 staining is usually negative. PCDLBCL-LT exhibits the gene expression profile of activated B-cell-like DLBCL, and fluorescence in situ hybridization analysis has revealed translocations involving c-MYC, Bcl-6, and IgH genes.

Conversely, secondary cutaneous lymphoma is a systemic disease accompanied by subsequent development of skin nodules upon presentation. Our patient was a middle-aged man with a history of gastric DLBCL. The subcutaneous nodules in his arms presented with no redness, swelling, or ulceration, which different from the presentation of PCDLBCL-LT. The subcutaneous nodules in his arms presented with no redness, swelling, or ulceration, which different from the presentation of PCDLBCL-LT. The nodules of this patient appeared over the arms, legs, and buttocks, which is also different from PCDLBCL-LT. IHC analysis of skin biopsy revealed the same expression profile as the primary gastric DLBCL, and we did not observe the strong Bcl-2, MUM1, or Foxp1 expression levels that are typically found in most PCDLBCL-LT patients. Primary CBCL is an indolent disease with a long clinical course and an excellent response to radiation therapy that successfully salvages recurrent disease even when the dose is as low as 4 Gy. Our patient was also treated with radiation therapy, but there was no effect. Although only skin infiltration was present according to the PET-CT scan, a diagnosis of secondary skin DLBCL was made.

Histone deacetylase inhibitors (HDACis) act by modifying gene expression and are the newest class of drugs demonstrated to be promising for patients with certain malignancies, including lymphoma. Multiple HDACis are currently under various clinical trial phases for treatment of several types of NHL, including DLBCL. Chidamide is a benzamide-type HDACi and acts by inducing growth arrest and apoptosis in blood- and lymphoid-derived tumor cells. Dong et al performed a phase I study of chidamide in patients with solid tumors and lymphoma. Four patients with T-cell lymphoma achieved a partial response (PR), and no dose-limiting toxicities were identified in the twice per week cohorts at up to 50 mg for 4 consecutive weeks. A phase II study enrolled 79 patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), and the results revealed that 11 (14%) patients achieved CR/Cru and 11 (14%) achieved a PR. Based on this pivotal study, chidamide was approved in China for management of relapsed and/or refractory PTCL. Altered HDAC expression has been described in multiple B- and T-cell malignancies, such as DLBCL, FL, and CLL. HDACs can be both overexpressed and underexpressed in DLBCL, and the overexpression is associated with good outcomes in DLBCL but with negative outcomes in PTCL.

According to the instructions of chidamide in PTCL patients, we also give the patient the same dose of chidamide (30 mg twice per week). Fortunately, the patient in this report responded well to chidamide and exhibited long-lasting CR. Our opinion is that relapsed/refractory secondary skin DLBCL, which does not respond well to the standard therapeutic options, can be treated with the chidamide. Further research and more cases are still needed to further validate its efficacy for patients with secondary skin DLBCL.

4. Ethics approval and informed consent

All clinical specimens were obtained with the approval of the institutional ethics committee, and the research was performed in accordance with the Declaration of Helsinki. Written informed consent for the publication of the patient’s clinical details and images was obtained from the relative of the patient.
Author contributions

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