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Case Report

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Successful Treatment of Idiopathic Multicentric Castleman Disease With Rash as the Initial Symptom Using a Rituximab-Based Regimen

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Abstract

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder characterized by enlarged lymph nodes and systemic inflammation, often involving multiple organ dysfunction. However, cutaneous involvement in iMCD is rare and heterogeneous, and studies on the treatment of iMCD with skin involvement are scarce. Here, we present a rare case of iMCD with prominent facial skin involvement, which showed significant improvement with rituximab-based regimen treatment.

Keywords: Castleman disease; Idiopathic MCD; Rash; Cutaneous; Rituximab; Bortezomib

Introduction

Castleman disease (CD) is a group of rare, heterogeneous lymphoproliferative disorders characterized by common pathological features on lymph node biopsy [1, 2]. Based on clinical manifestations and the extent of lymph node involvement, CD is classified into unicentric CD (UCD) and multicentric CD (MCD). UCD is a localized and reversible condition, whereas MCD is systemic, progressive, and potentially fatal [2]. Patients with MCD typically present with systemic inflammatory symptoms including fever, weight loss, anasarca, night sweats, cytopenia, and life-threatening organ dysfunction [2-4]. Skin involvement, as an extranodal manifestation of MCD, is rare [2]. This report presents a rare case of MCD with initial facial cutaneous involvement that showed significant improvement following treatment with a combination of RVD regimen (rituximab, bortezomib and dexamethasone).

Case Report

A 47-year-old male presented to our hospital with a 1-year history of facial rash and a 9-month history of hematuria and proteinuria. He had been treated with pimecrolimus for his rash and glucoside tripterygium for renal dysfunction for over 4 months, with limited efficacy. Family medical history was unremarkable. Physical examination revealed multiple reddish-brown pigmented areas with ill-defined margins on the face, some coalescing into patches (Fig. 1a). Laboratory studies showed normal blood routine examination, elevated inflammatory index (C-reactive protein: 12.43 mg/L, reference range (RR): 0 - 8 mg/L; erythrocyte sedimentation rate (ESR): 81 mm/h, RR: < 20 mm/h), elevated globulin (53.8 g/L, RR: 20 - 40 g/L), and normal renal function (serum creatinine (Cr): 75 µmol/L, RR: 57-97 µmol/L; estimated glomerular filtration rate (eGFR) 103.1). Serum levels of free light (FL) chain kappa (795 mg/L, RR: 170 - 370 mg/L) and lambda (465 mg/L, RR: 90 - 220 mg/L) were increased, and the FL chain ratio was normal (1.71). Serum protein electrophoresis revealed elevated gamma globulin levels (34.8 g/L, RR: 11 - 21 g/L), while both blood and urine immunofixation electrophoresis were negative. Among the immunoglobulins (Igs), IgG was significantly elevated (3,018 mg/dL, RR: 860 - 1,740 mg/dL). The urinalysis indicated proteinuria (+) and hematuria (++). Random urine protein was 0.419 g/L (RR: 0.01 - 0.14 g/L), and the urine protein-to-creatinine ratio was 0.63 g/g (RR: 0 - 0.2 g/g). Cellular cytokine testing showed elevated interleukin (IL)-6 levels (IL-6: 15.9 pg/mL). Tests for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), cryoglobulins, and the Coombs test were all negative. Hepatitis B and C viruses, syphilis, and human immunodeficiency virus (HIV) antibodies were all negative. Ultrasound revealed

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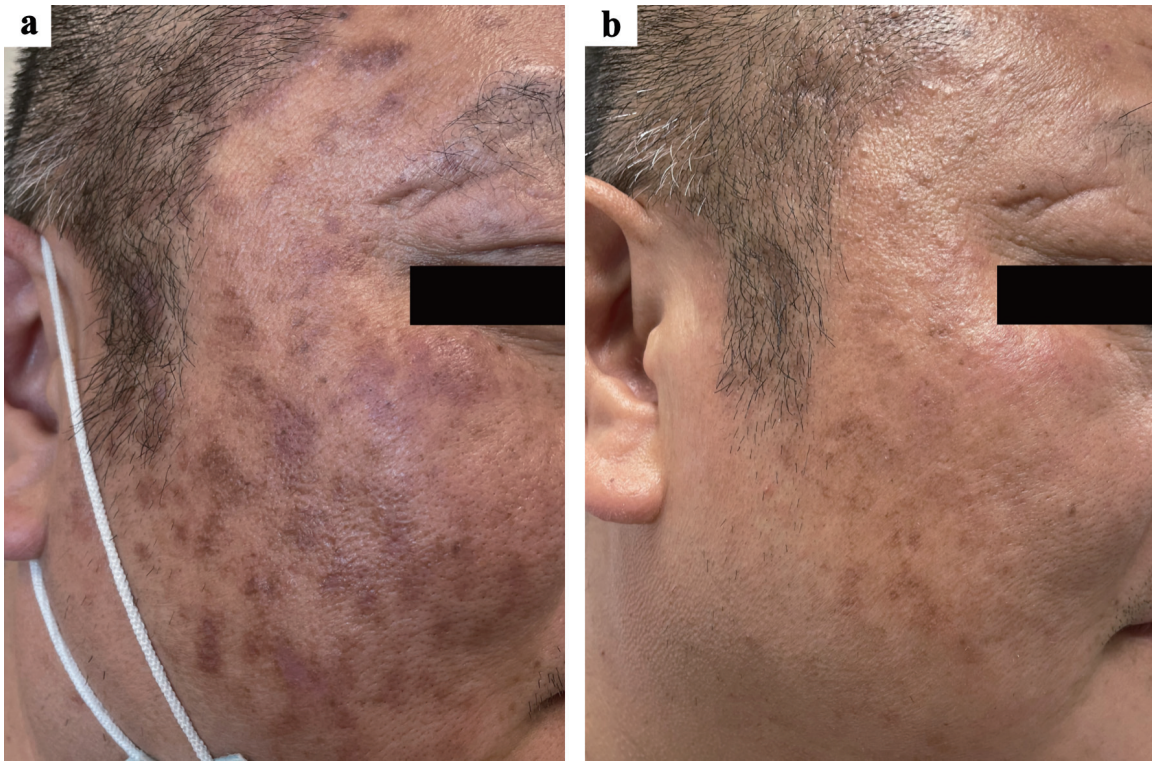

Figure 1. (a) Multiple areas of reddish-brown pigmentation can be seen on the patient's face, with ill-defined margins on the face, some coalescing into patches. (b) After eight cycles of the RVD regimen (rituximab, bortezomib and dexamethasone), the patient' cutaneous rash showed significant improvement along with the systemic improvement of CD. CD: Castleman disease.

multiple enlarged lymph nodes in the bilateral axillary (largest 3.9 × 1.0 cm) and inguinal regions (largest 2.6 × 1.0 cm), with clear borders and distinct corticomedullary differentiation. No other enlarged lymph nodes were observed in the chest or abdomen. No abnormalities were detected in the heart or lungs, and neurological examination was unremarkable.

A skin biopsy was performed, and pathological analysis revealed infiltration of monocytes around blood vessels in the dermis, appendages, and perineural fat lobules, with an increased number of plasma cells. Immunohistochemical staining was positive for CD20, CD138, IgG, and IgG4 (Fig. 2a-c). The renal biopsy results indicated focal nephritis (sclerosing type) with small foci of inflammatory cell infiltration in the interstitium. The bone marrow biopsy indicated hyperplastic hematopoietic tissue with an increased number of reactive plasma cells. Immunohistochemistry revealed weak CD19 positivity, CD38 positivity, and expression of lambda, kappa, and multiple myeloma oncogene 1 (MUM1). CD20, CD3, and CD56 were not expressed. No clonal rearrangement of the IgH gene was observed. The patient subsequently underwent an excisional biopsy of a cervical lymph node, which revealed active hyperplasia of lymphoid tissue with a marked increase in plasma cells. Immunohistochemical staining results were similar, showing positivity for CD20, CD138, IgG, and IgG4, with an IgG4/IgG ratio of no more than 40%. Stain for human herpes virus-8 (HHV-8) was negative (Fig. 3a-d).

By combining systemic presentations, laboratory "flare" markers, histopathologic findings in lymph nodes, and cutaneous involvement, the diagnosis of idiopathic multicentric Castleman disease (iMCD) was made [2]. The patient received eight cycles of the RVD regimen (rituximab, bortezomib, and dexamethasone) from November 2022 to April 2023, achieving a partial response (PR) [2]. Intriguingly, along with the systemic improvement of CD, his cutaneous rash also showed significant improvement (Fig. 1b). Maintenance therapy with rituximab was administered for an additional 6 months. The patient is currently under regular follow-up, with the disease stable.

Discussion

In previously reported cutaneous involvement in CD, skin presentations varied, including paraneoplastic pemphigus, erythema brown papules, plaques, and/or nodules, and purpura/vasculitis [5, 6]. Paraneoplastic pemphigoid is more likely to appear as retroperitoneal UCD, while MCD with the plasma cell (PC) pathological type tends to develop papules, plaques, and nodules [6]. However, due to the limited sample size, definitive risk factors for skin manifestations in CD remain unclear. Dermal lymphoid follicles with nodal infiltration of lymphoid and plasma cells may be a key characteristic of "CD-like" skin changes. In a retrospective study of 25 CD patients, nearly all with MCD exhibited dermal inflammatory infiltration predominantly composed of lymphocytes and plas-

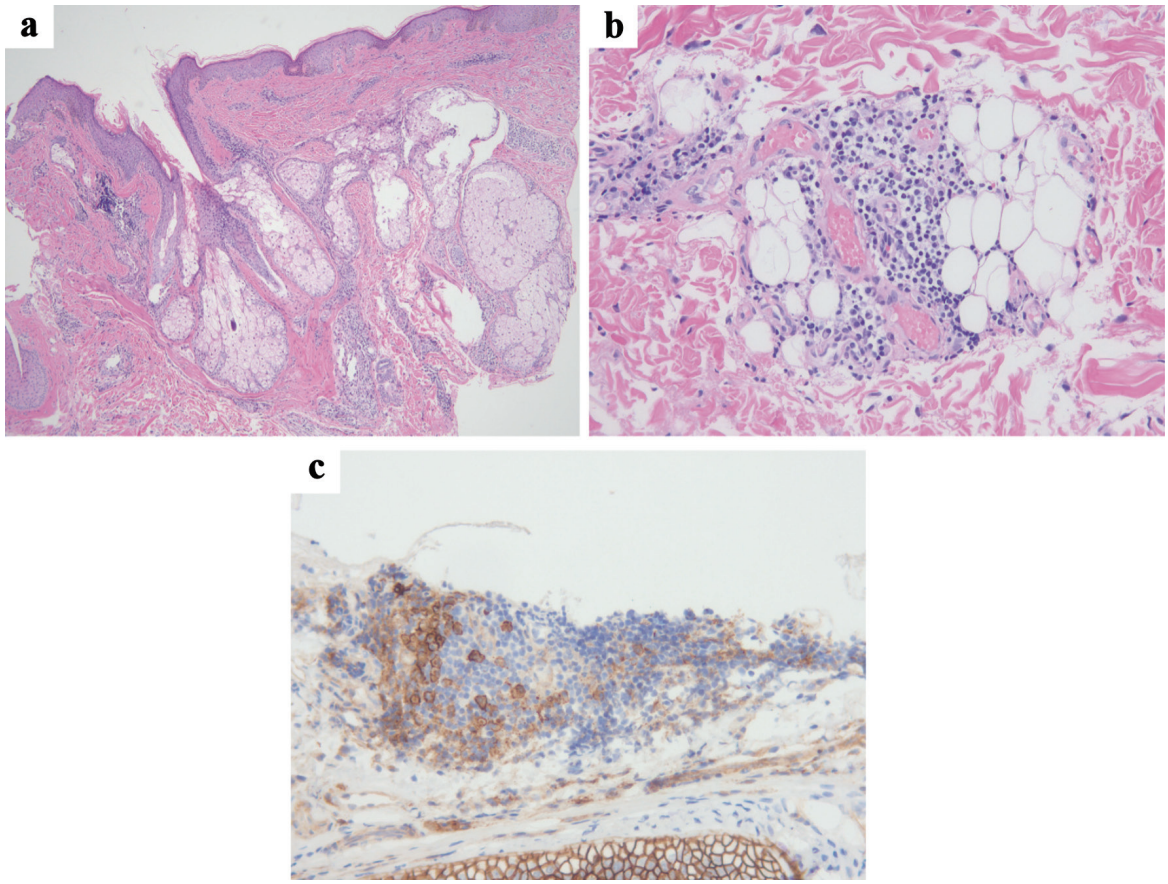

Figure 2. (a) Lymphoid cell infiltration around the skin appendages (H&E stain, × 40). (b) High-power view showed most of cells are mature plasma cells (H&E stain, × 100). (c) CD138 staining showed the infiltration of (small clusters) of plasma cells (immunohistochemistry, × 200). H&E: hematoxylin and eosin.

ma cells, with histiocytes, eosinophils, and neutrophils rarely found [7].

Cutaneous/systemic plasmacytosis (C/SP) is a plasma cell disorder characterized by reddish-brown patches, lymphadenopathy, and hypergammaglobulinemia. Histopathologically, C/SP shows dense perivascular infiltrates of mature plasma cells, lymphocytes, and mast cells, along with basal epidermal hyperpigmentation and an increase in dermal blood vessels. There have been reports of pathophysiological overlap between C/SP and iMCD, suggesting potential similarities in their pathogenesis [8]. Chen et al described a 35-year-old Chinese woman who gradually developed dark brown papules, patches, and plaques with mild pruritus over more than 4 years. A skin biopsy revealed reactive lymphoid follicular hyperplasia within the dermis and subcutaneous tissue, surrounded by numerous mature plasma cells with Russell body formation, and she was eventually diagnosed with plasmacytic variant of idiopathic multicentric CD (PMCD) [6]. Drissi et al described a 46-year-old woman who was finally diagnosed with iMCD. She presented with dark spots concentrated over her chest and back for more than 7 years. A biopsy of a lesion showed a dense nodular mixed infiltrate with plasma cells and melanophages, suggestive of cutaneous lymphoid hyperplasia [9]. In a study comparing 15 cases of iMCD with 69 cases of C/SP, no statistically significant differences were observed in the histopathological features of the skin between the two conditions [10]. Indeed, most of the skin infiltrates in iMCD were indistinguishable from those in C/SP [11].

Interestingly, our patient exhibited cutaneous manifestations 1 year prior to the final diagnosis of iMCD, with only limited relief from topical treatments. The patients subsequently exhibited more aggressive renal dysfunction and a high inflammatory status. Later findings of constitutional systemic symptoms, lymph node and skin biopsy results, combined with abnormal laboratory tests (anemia, hypergammaglobulinemia, elevated ESR, CRP, and IL-6), confirmed the final diagnosis of plasmacytic variant MCD. Given the unsatisfactory response to nonspecific treatments, the prolonged disease course, and the clear correlation between the skin rash and iMCD, we propose that the cutaneous findings were part of the systemic involvement of iMCD. Previous sporadic cases have similarly reported cutaneous involvement preceding other organ involvement in iMCD [6, 8, 9 10], suggesting that early skin manifestations may serve as a precursor to more extensive systemic disease.

For iMCD patients, regardless of disease severity, the only US Food and Drug Administration (FDA)-approved treatment

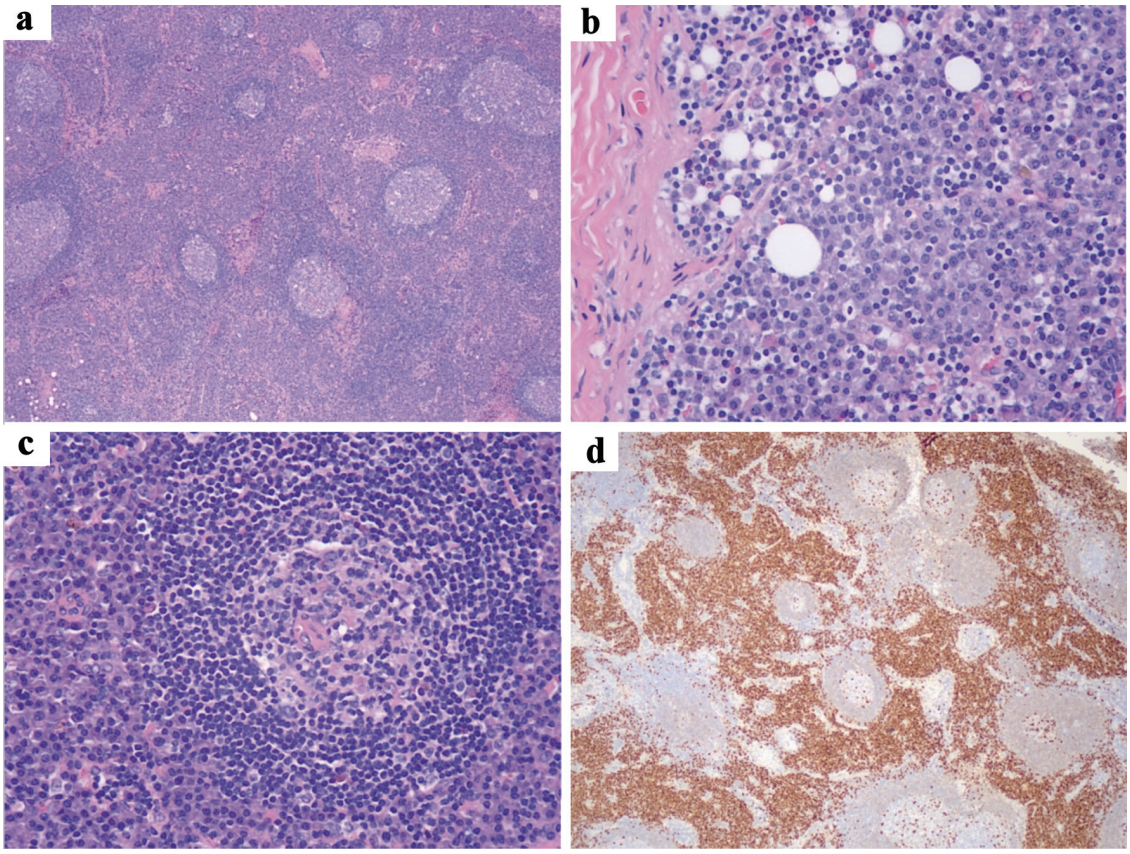

Figure 3. (a) Low-power view showed lymph follicles of varying size with a retained mantle zone and a diffuse expansile infiltrate of basophilic cells in the paracortical regions (H&E stain, × 40). (b) High-power view showed diffuse plasma cell hyperplasia extending to the subcapsular region of the lymph node (H&E stain, × 200). (c) High-power view showed a slightly atrophic follicle with thickening of the mantle zone (H&E stain, × 200). (d) MUM1 staining showed diffuse plasma cell hyperplasia (immunohistochemistry, × 40). H&E: hematoxylin and eosin.

tested in a randomized trial for iMCD is siltuximab, an IL-6 antagonist [12]. Tocilizumab, an anti-IL-6 receptor antibody, was approved for iMCD in Japan [13]. In December 2021, siltuximab was officially introduced in mainland China by the National Medical Products Administration of China (NMPA). For patients not approachable to siltuximab, or those who may not respond to IL-6 therapies, therapeutic alternatives varied, including rituximab with or without chemotherapy, and other agents like proteasome inhibitors and immune modulators. In the national study, Li et al has introduced multiple treatment regimens applied in China [1]. In our previous research, we have innovatively applied RVD regimen (rituximab, bortezomib and dexamethasone) in iMCD patients and achieved satisfying response and great tolerability [14]. In this case, due to the unavailability of siltuximab, the patient received eight cycles of the RVD regimen and subsequently underwent rituximab maintenance therapy at our center, achieving significant clinical improvement. Notably, with the control of systemic inflammation, marked improvements were observed in renal function, hematopoietic function, and skin lesions, further supporting the close association between cutaneous manifestations and CD.

Due to the rarity of the disease and the infrequency of skin involvement, systematic studies on cutaneous manifestations in CD are challenging. Early identification of the dermatopathological features of CD is crucial, especially for patients presenting with initial skin manifestations. In this study, we present an intriguing case of iMCD with skin involvement. Our findings enhance the understanding of cutaneous manifestations in CD and provide valuable insights for its diagnosis and treatment.

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None to declare.

Financial Disclosure

No funding was received for this research.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions

LZ wrote the manuscript. YL and LSY revised the article and created the charts. FY conducted a pathological diagnosis. HYT and HTM formulated the treatment plan. LSY, XJY and QMY managed the treatment process for the patient. All authors approved the submitted version of the paper.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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