

Spotlight on Clinical Response

Cutaneous castleman's disease responds to anti-interleukin-6 treatment

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Abstract

Castleman's disease is uncommon, and cutaneous involvement is even rarer. We report a 42-year-old Asian woman with the multicentric plasma cell variant of Castleman's disease limited to her skin. The literature suggests that Castleman's disease is driven by interleukin-6 (IL-6). Based on these data, we hypothesized that suppression of IL-6 would have a salutary effect. Therefore, our patient was treated with CNTO328, a chimeric murine anti-human IL-6 antibody. She has shown a remarkable, ongoing response to this treatment, with almost complete clearing of her skin lesions after six doses. [Mol Cancer Ther 2007;6(9):2386–90]

Introduction

Castleman's disease is a B-cell lymphoproliferative disorder characterized by lymph node hyperplasia with vascular proliferation. This disorder is quite uncommon, and cutaneous involvement is even rarer. We report the characteristics and successful treatment of a 42-year-old Asian

woman participating in a phase I study using CNTO328 [an interleukin-6 (IL-6) antibody]. The patient had the multicentric plasma cell variant of Castleman's disease limited to her skin without any evidence of systemic involvement. The literature on this condition is also reviewed.

It has been suggested that cutaneous Castleman's disease and cutaneous plasmacytosis represent the same disease. These disorders are difficult to diagnose. However, accurate diagnosis may be especially important because increased production of IL-6 by lymphoid tissue has been implicated as a pathogenic mechanism (1). Of interest, therefore, is that our patient with cutaneous Castleman's disease showed a rapid response to a chimeric murine anti-human IL-6 antibody (CNTO328).

Case Report

A 42-year-old Asian woman presented to us with a 7.5-year history of multiple plaques and nodules on the face and chest. She had been seen by several physicians who found it difficult to diagnose her condition. The patient had no other complaints or associated systemic symptoms. In particular, she had no fever, malaise, or weight loss. Her physical exam was unremarkable except for multiple erythematous nodules on the face and chest (Fig. 1). No lymphadenopathy or visceromegaly was identified. The laboratory data showed hemoglobin of 14.7 g/dL, WBC count of 5,300/ μ L, and platelet count of 233,000/ μ L. Blood workup was remarkable for elevated levels of total protein (9.0 g/dL), immunoglobulin G elevated at 1,890 mg/dL (upper limit of normal, 1,600 mg/dL), and immunoglobulin M nearly elevated at 227 mg/dL (upper limit of normal, 230 mg/dL). Serum electrolytes were normal. Computed tomograms of the chest, abdomen, and pelvis were negative for any evidence of disease. HIV screening was negative.

A skin biopsy was taken from a right submental lesion (Fig. 2). It showed a superficial confluent infiltrate of lymphocytes and plasma cells located predominantly around the vessels in the upper dermis and a nodular aggregate of lymphoid and plasma cells in the deep dermis. A biopsy from the right axilla showed similar changes in the dermis. Cluster of differentiation (CD)-3 and CD20 were similarly expressed implying approximately equal numbers of T and B cells, respectively. CD4⁺ T cells predominated over CD8⁺ T cells in a ratio of ~3:1. κ and λ stains showed a mixed plasma B-cell population. PCR testing was negative for human herpes virus-8. Review of pathology by our dermatopathologists (J.A.T. and P.R.C.) confirmed the diagnosis of cutaneous Castleman's disease

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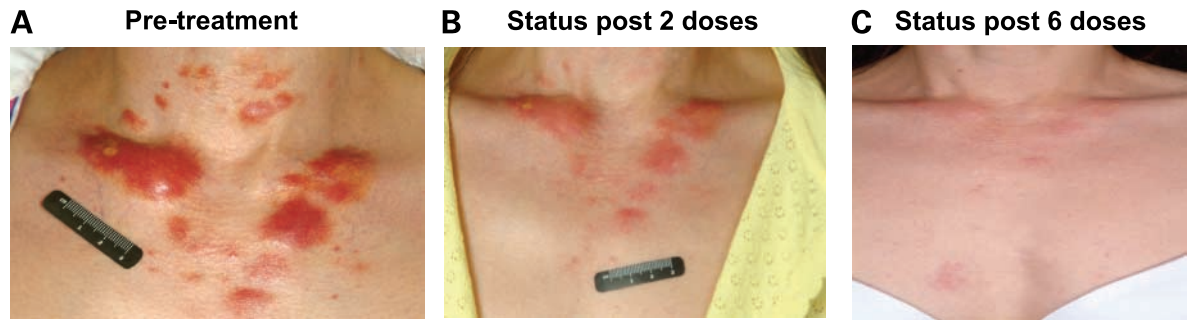


Figure 1. **A**, multiple erythematous nodules and plaques on the lower face and neck (pretreatment). **B**, marked decrease in the size and number of lesions (after two doses of anti-IL-6 antibody CNTO328). **C**, almost complete clearing of the lesions (after six doses of anti-IL-6 antibody CNTO328).

(multicentric plasma cell variant) without any evidence of systemic involvement.

She was initially treated with rituximab, valacyclovir, and azathioprine without significant clinical improvement. Subsequently, there was progressive slow growth of the cutaneous tumors. Treatment with Plaquenil (2 months), minocycline (two courses of 2 months each), doxycycline (two courses of 2 months), prednisone (two tapering courses of 1 month each), and intralesional triamcinolone to two lesions failed to benefit her.

The patient was eventually treated with CTNO328, a chimeric murine anti-human IL-6 antibody. She experienced no significant side effects and noted improvement in

her skin lesions within 24 h. With each subsequent dose, improvement continued. After six doses, skin lesions had almost disappeared (Fig. 1). She continues to exhibit no side effects, and, being an avid athlete, often runs up to 5 miles within 24 h after each dose of treatment.

Materials and Methods

After signing informed consent per guidelines of the Institutional Review Board at M.D. Anderson Cancer Center, the patient was treated with CTNO328, an experimental chimeric murine anti-human IL-6 antibody (Centocor R&D, Inc.), at an i.v. dose of 12 mg/kg every 3 weeks (this patient was treated as part of a phase I clinical trial).

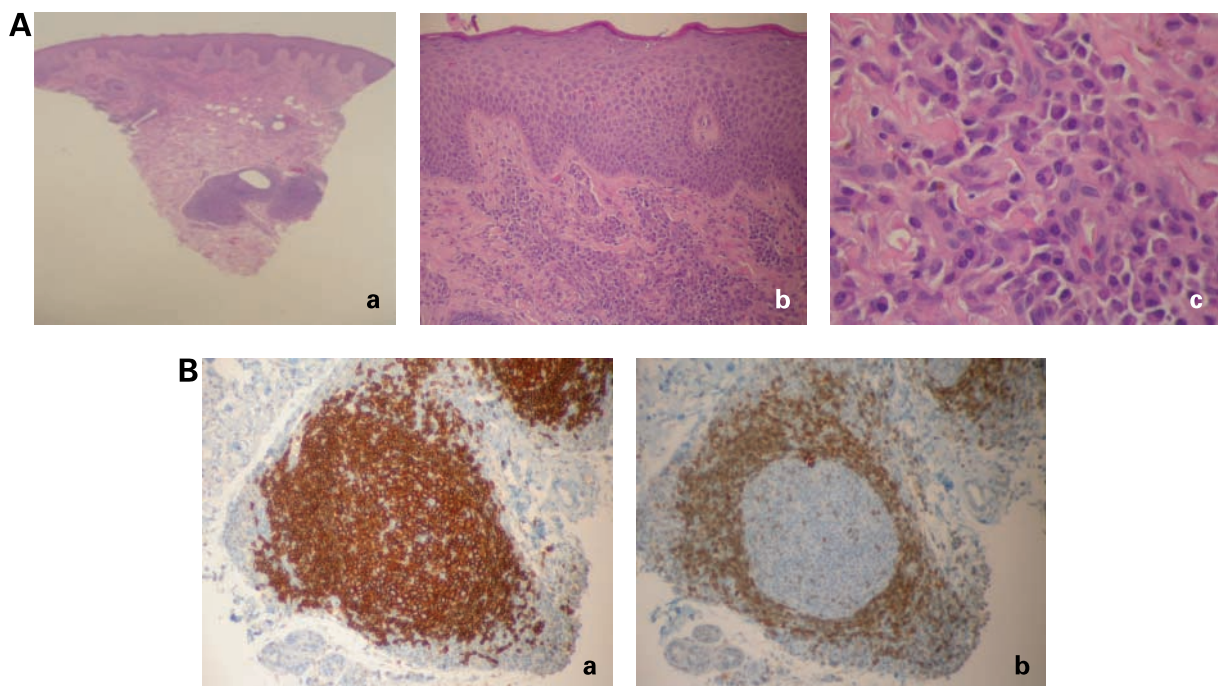


Figure 2. **A**, **a**, low-power view of skin biopsy shows a superficial confluent infiltrate and a deep nodular aggregate. **b**, the superficial confluent mononuclear infiltrate is present in the papillary and upper reticular dermis. There is no epidermotropism of the mononuclear cells in the dermis into the overlying acanthocytic epidermis. **c**, high magnification of the infiltrate shows numerous plasma cells with few lymphocytes. No atypicality of the cells is seen (H&E: **a**, $\times 2$; **b**, $\times 20$; **c**, $\times 40$). **B**, **a**, a nodular aggregate of B cells (CD20⁺) in the deep dermis. **b**, T cells (CD3⁺) infiltrate around the nodule of B cells (immunoperoxidase stain: **a**, $\times 10$; **b**, $\times 10$).

To date, she has received a total of six treatments. The response was assessed on physical examination as well as by serial photographs (Fig. 1).

We did a PubMed literature search to find all reported cases of patients with cutaneous Castleman's disease as well as those with cutaneous plasmacytosis because these diseases are believed to represent one entity. We reviewed their characteristics, response to therapy, and outcome.

Results

Our patient first noted improvement within 1 day after CNTO328. Resolution of skin lesions continues with each subsequent dose. CNTO328 was well tolerated and this patient has shown no significant short-term or long-term side effects.

In reviewing the world literature, we found a total of five cases of cutaneous Castleman's disease (including ours; refs. 2–5) and 26 cases of cutaneous plasmacytosis (6–22). Both cutaneous Castleman's disease and cutaneous plasmacytosis were overwhelmingly more common in Asians, who comprised 79% of cases, and associated with polyclonal elevation of immunoglobulins.

Taken together (cutaneous Castleman's and cutaneous plasmacytosis), there are a total of 22 of 31 (71%) patients described who have isolated cutaneous disease. Patients with cutaneous disease are similar to those with extracutaneous manifestations in that they have a median age in their mid to late 50s at diagnosis, are primarily Asian, and are predominantly men. Both groups had frequent polyclonal elevation in immunoglobulins (68% versus 89% in patients with isolated cutaneous disease versus those with extracutaneous manifestations, respectively). Based on current data, it is not possible to know whether or not

there is a difference in survival because the vast majority of all patients with available data were still alive at the time that they were reported. The median survival of patients with isolated cutaneous involvement has not been reached after a median follow-up of 36 months, whereas the median survival of patients with extracutaneous manifestations has not been reached after a median follow-up of 17 months. Three patients developed other malignancies. They included T-cell lymphoma ($n = 1$; ref. 8), lung and anal cancer ($n = 1$; ref. 15), and gastric cancer ($n = 1$; ref. 18). All of these patients had solely cutaneous disease.

Discussion

Castleman's disease is a lymphoproliferative disorder that was first described by Dr. Benjamin Castleman in 1956 in a series of 13 patients who had mediastinal lymph nodes which histologically resembled Hassall's corpuscles of the thymus (23). The disease has been divided into two clinical entities: unicentric and multicentric. It can also be classified histologically into three types: hyalinized vascular, plasma cell, and a mixed variant. The hyalinized vascular type is more common (90%) and presents in a younger age group. It is commonly unifocal, usually originating in the mediastinum. The plasma cell variant is less common (10%) and mostly multicentric. It is usually far more aggressive, presenting in older patients with generalized lymphadenopathy, hepatosplenomegaly, systemic symptoms, and polyclonal increase in immunoglobulins, and is associated with a poorer prognosis.

In the search for a unifying pathogenesis of Castleman's disease, IL-6 has emerged as a key factor. Circulating IL-6 levels are high in patients with Castleman's disease, and furthermore, deregulated production of IL-6 in mice

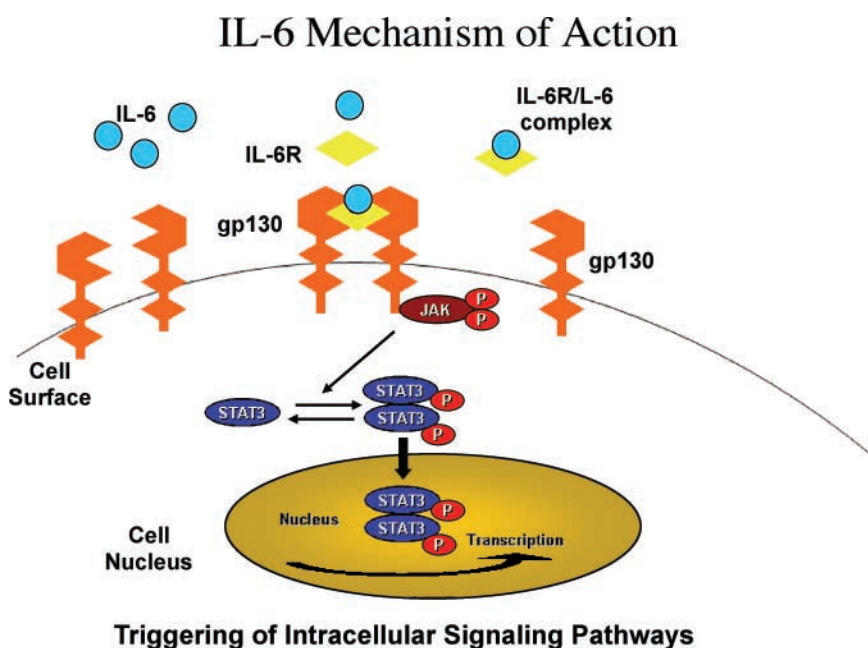


Figure 3. IL-6 mechanism of action. IL-6 functions by binding to either its membrane-bound receptor or its soluble receptor. The binding of IL-6/sIL-6R to the gp130 signaling subunit induces the homodimerization of gp130. This, in turn, triggers an intracellular signaling cascade through several pathways including Ras/Raf, mitogen-activated protein kinase, and Janus-activated kinase (JAK)/signal transducers and activators of transcription (STAT).

produces a syndrome closely resembling Castleman's disease (1). The production of IL-6 in Castleman's disease has been found to be in close proximity to blood vessels and B lymphocytes, resulting in effects on angiogenesis and plasma cells (24). Of interest, human herpes virus-8 seems to be universally present in cases of multicentric Castleman's disease with HIV and sporadically present in those without HIV. Our patient was HIV seronegative, had multiple skin lesions of Castleman's disease, and did not show the presence of human herpes virus-8. Human herpes virus-8 has been shown to produce a viral analogue of IL-6 with close similarity to the human IL-6, suggesting a common final pathway in the pathogenesis of multicentric Castleman's disease. IL-6 is also aberrantly produced and can function as an autocrine or paracrine growth factor in other cancers as well, and it is a biologically and prognostically important cytokine in many lymphoid malignancies (25).

Castleman's disease is an uncommon disease and therefore may create a diagnostic dilemma for clinicians, as it initially did in our patient. Other lymphoproliferative disorders need to be ruled out. The diagnosis is based on clinical features in the presence of follicular architecture with an interfollicular plasma cell-rich infiltrate and proliferation of small hyalinized vessels seen on pathology. The high likelihood of multicentric disease in the plasma cell variant implies that physicians should perform clinical staging studies such as computed tomography scans to look for disease elsewhere. In our patient, the staging studies failed to reveal radiological evidence of extracutaneous disease.

In comparison with unicentric Castleman's disease, in which surgery has proved to be the primary and possibly curative treatment, there is no gold standard for the treatment of multicentric Castleman's disease. A variety of approaches including surgery, radiation, steroids, antiviral therapies, specific antibodies, and chemotherapy have been tried in multicentric Castleman's disease with variable results. Our patient showed minimal response to the anti-CD20 antibody (rituximab) and no response to azathioprine.

Because deregulated production of IL-6 by B cells is a key pathogenic factor for Castleman's disease, blockade of this cytokine is an attractive therapeutic approach. Our patient showed a rapid response to this treatment, with initial improvement noted within 24 h after the first dose and then ongoing resolution of lesions with each subsequent dose (Fig. 1). She has had no significant side effects due to the therapy. This is consistent with our observations in six other patients with Castleman's disease who have tolerated treatment with CNTO328 in doses up to 12 mg/kg i.v. every 3 weeks (26). No specific dose-limiting toxicity or allergic reactions were observed with repeated dosing. Preliminary studies in these patients suggested that CNTO328 can abrogate the effects of IL-6 and can induce both clinical and biochemical improvement in patients with Castleman's disease (26). Of interest, a study in Japan by Nishimoto et al. (27) shows that humanized anti-IL-6

receptor monoclonal antibody (tocilizumab) also improves symptoms and biochemical abnormalities in patients with multicentric Castleman's disease.

IL-6 is a pleiotropic cytokine with multiple downstream effects that regulate key signaling pathways (Fig. 3). How activation of these pathways triggers the phenotypic features of Castleman's disease deserves further investigation. However, it is clear that this rare disorder is of special interest because of our current understanding that a key underlying defect driving it is aberrant production of IL-6 and the salutary effects of emerging therapies targeting IL-6.

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