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Case Report

Unicentric Castleman's Disease with Multicentric Behavior: A Case Report

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Abstract

Castleman's disease is a clinicopathological entity associated with lymphoproliferation. We report a case of a 13-year-old who was initially clinically suspected to have Behçet Disease (BD) (owing to clinical features at presentation), though was later histologically confirmed to have Castleman's disease. This case report shows how unicentric Castleman's disease can share behaviors similar to the multicentric disease.

Keywords: *Unicentric Castleman Disease; Behçet Disease; Paraneoplastic Syndrome*

Introduction

Castleman's disease (CD) is a group of lymphoproliferative disorders of uncertain cause, mainly presenting lymphadenopathy; histologically as well as prognostically, it is different from malignant lymph-node hyperplasia [1]. Castleman., *et al*. had first described the disease in a group of patients with benign localized hyperplastic lymph nodes in 1956 [2]. Unicentric or localized Castleman disease (UCD) and systemic or multicentric Castleman disease (MCD) are the two well-defined clinical subtypes, while the plasma cell type, hyaline vascular type and mixed type are the three main histological variants [3,4]. The etiology of CD is still unclear; however, the disease's epidemic had arisen with the human immunodeficiency virus (HIV), and a relationship with other viruses and diseases was later reported: human herpesvirus-8 (HHV-8), autoimmune diseases and malignancies. An international collaborative working group has recently proposed a novel classification, referred to as idiopathic MCD (iMCD), where all associated viruses are negative [5]. The incidence of UCD was estimated to be 15.9 to 19.1 cases per million person-years, using two commercial claims databases [6]. UCD shows a slight predominance in females (1.4:1), and the mean age for diagnosis is 34 years; the optimal approach for treating UCD is by complete surgical resection, which has an excellent prognosis, with an estimated 10-year survival rate of 95% [7].

Case Presentation

A 13-year-old child was referred to pediatric immunology and rheumatology clinic at Queen Rania Children's Hospital with a history of severe stomatitis and suspected case of Behçet Disease (BD) that was extremely resistant to therapy. He had no past medical history

of note. Firstly, he presented to outpatient clinics with acute onset of oral and genital ulcers of one-month duration and was treated as viral stomatitis. He was then admitted for systemic antiviral and antifungal therapy for two weeks and underwent further investigations. Upper endoscopy revealed oral ulcers, severe Gastroesophageal reflux esophagitis, esophageal and gastric ulcers grossly. Biopsy showed reflux type esophagitis. Lower endoscopy revealed mild colitis and the biopsies did not have any diagnostic findings. After the previous whole investigations, he was labeled to have BD; consequently, he was prescribed colchicine and systemic steroids for a total of 2 weeks duration with no response. He lost 17 Kilograms during the disease process. Upon his arrival to our clinic, the patient was found to have multiple crusted hemorrhagic ulcers covering the buccal mucosa, palate and gingiva with extensive blackish lip crusts (Figure 1). Routine investigations such as full blood count and biochemical profile were found to be within normal range except for raised ESR 77 mm/hour, and mild fecal calprotectin elevation, HHV-8 serology IgM was undetectable (Table 1). The patient was also complaining of severe abdominal pain and abdominal ultrasound showed a large lobulated hyperechoic mass lesion in the periportal region reaching the head of the pancreas and down to the right suprarenal region causing compression on gall bladder measuring about 8x50 cm. He was admitted to the hospital on this regard for further evaluation. Abdomen and pelvic computerized tomography scan (CT scan) with intravenous contrast showed that the mass is just superior to the right kidney, not crossing the midline without any evidence of thrombosis or lymph node enlargement (Figure 2). CT scan of the brain and chest did not show any abnormal findings. Biopsies from the buccal area and CT guided biopsy of the abdominal mass were done. Buccal biopsy showed a benign salivary gland with sparse chronic inflammatory cell infiltrate, while CT guided biopsy showed benign lymphoid tissue with no evidence of malignancy. The patient then underwent surgical excision of the mass. Histopathology of the resected mass gave the diagnosis of Unicentric Castleman Disease (UCD), the hyaline vascular type (Figure 3). He continued to have the same disease manifestations postoperatively; severe abdominal pain, same oral mucosal ulcers, vomiting and inability to eat. The patient received intravenous methylprednisolone pulses 20 mg/kg for 5 days in addition to Azathioprine and was discharged on prednisolone 2 mg/kg with tapering plan, he showed impressive improvement around 80% (Figure 4). Upon steroid tapering, the patient was re-admitted as he developed a flare up, with exacerbation of oral ulcers and vomiting. The patient received IV methylprednisolone 2 mg/kg and Azathioprine dose had maximized, which was stopped due to side effects like raised transaminases and cytopenias then we replaced it by Cyclosporine. Patient is being followed at our clinic, he sustains remission for an 18 months while on low-dose prednisolone 10 mg daily and cyclosporine, we are trying to tail steroids off gradually to avoid disease flare.

Test	Result
ESR	77 mm/hour
ANA	1/80
Anti-dsDNA	Negative
ENA	Negative
ACL IgM, IgG	Negative
ANCA (MPO, PR3)	Negative
IgG	1422 mg/dl
IgM	105 mg/dl
IgA	165 mg/dl
IgG4	98 mg/dl
C3	197 mg/dl
C4	38 mg/dl
Ferritin	104 ng/mL
HHV-8 IgM	Undetectable
HIV serology	Negative
CMV PCR	Negative
EBV PCR	Negative
Fecal CALPROTECTIN	180 µg/g

Table 1: *Baseline Laboratory Values.*

Abbreviations *ESR: Erythrocytes Sedimentation Rate; ANA: Antinuclear Antibody; Anti-Dsdna: The Anti-Double Stranded DNA; ENA: Extractable Nuclear Antigen; ACL: Anti- Cardiolipin; ANCA: Antineutrophil Cytoplasmic Antibodies; Ig: Immunoglobulin; C3: Complement 3; C4: Complement 4; HHV-8: Human Herpes Virus 8; HIV: Human Immunodeficiency Virus; CMV: Cytomegalovirus; EBV: Epstein Barr Virus*

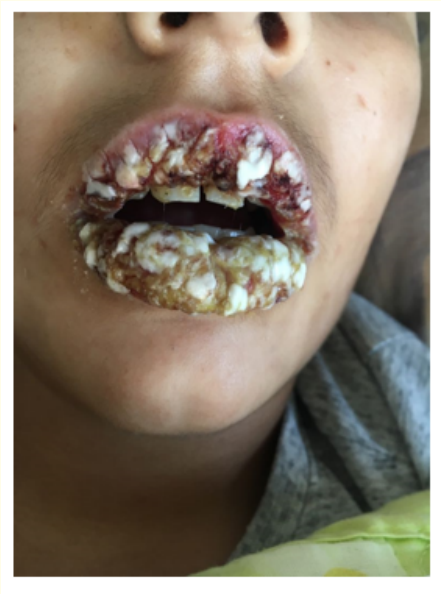

Figure 1: *Multiple crusted hemorrhagic ulcers covering the buccal mucosa, palate and gingiva with extensive blackish lip crusts.*

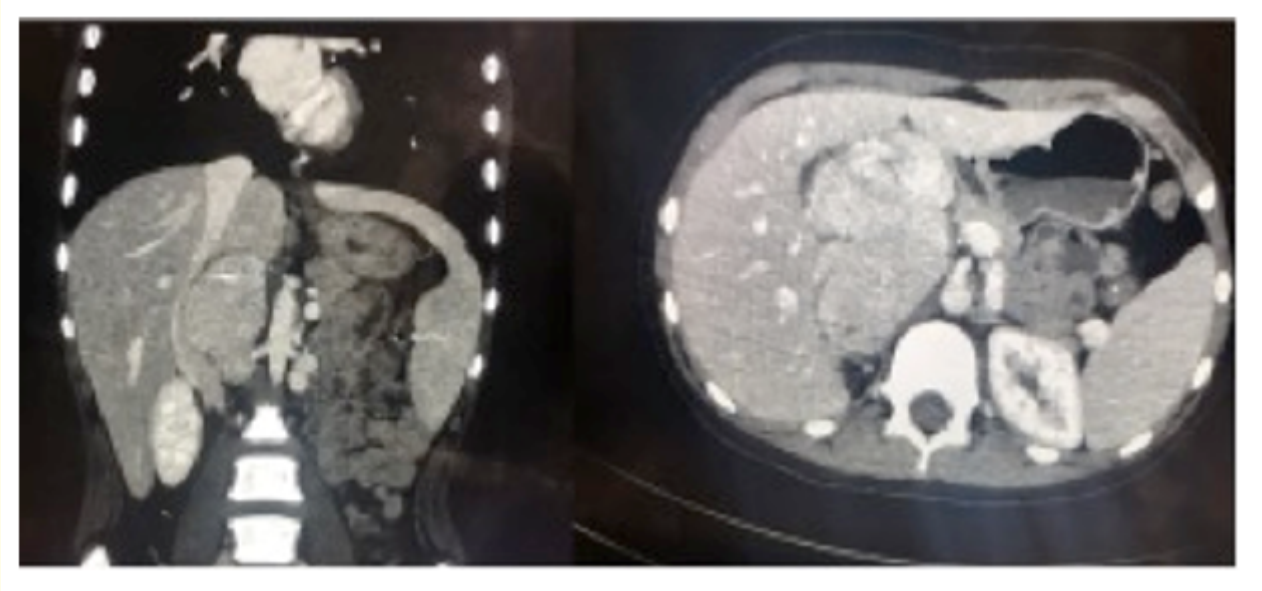

Figure 2: *Abdomen and pelvic C.T scan with I.V contrast showed that the mass is just superior to the right kidney, not crossing the midline with any evidence of thrombosis or lymph node enlargement.*

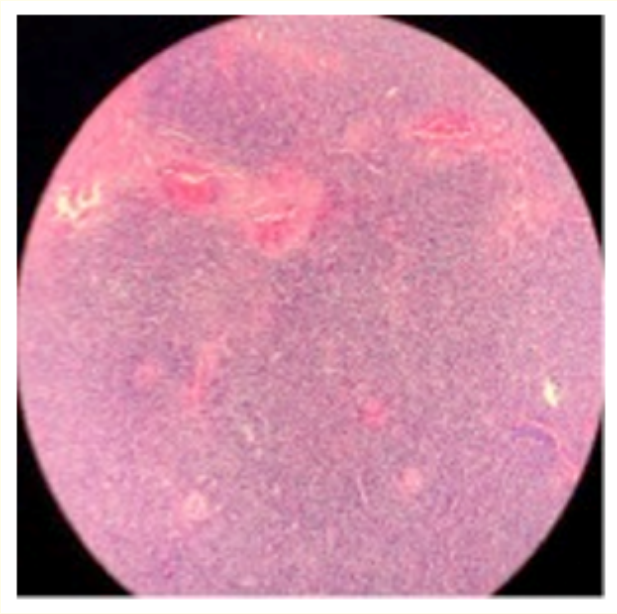

Figure 3: *Histopathology of the resected mass gave the diagnosis of Unicentric Castleman disease, the hyaline vascular type.*

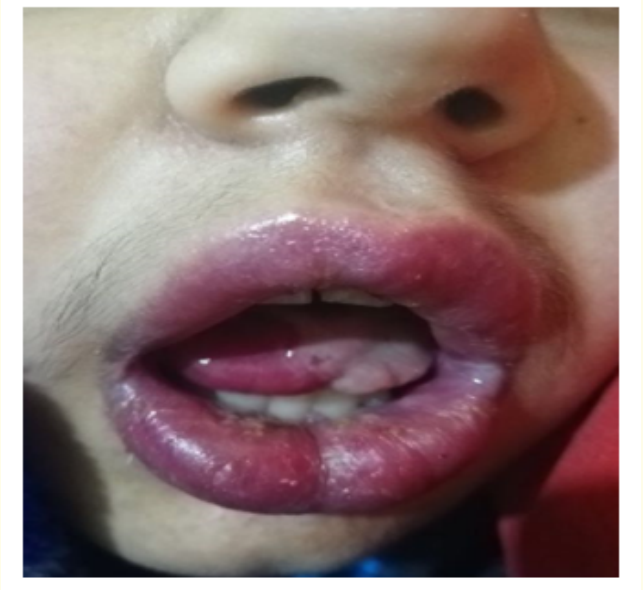

Figure 4: *The patient showed significant improvement after receiving I.V methylprednisolone for 6 doses in addition to azathioprine.*

Discussion and Conclusion

Castleman disease (CD), is a rare non-neoplastic lymphoproliferative disorder that characterized by angiofollicular lymph-node hypertrophy histologically. CD has two well-defined subtypes; unicentric (UCD) is typically localized, indolent, and often treated with localized therapy alone, or multicentric (MCD) is a systemic condition associated with heterogeneous symptoms and is usually treated with systemic therapies [8]. With a review of medical literature in existence, this case report attempts to show a different behavior of the UCD that clinically imitates an MCD.

The optimal approach for UCD is complete surgical resection and it has an excellent prognosis, with an estimated 10-year survival rates of 95% [6]. In our case, although UCD lesion underwent complete surgical resection, patient failed to respond, Li Yu*., et al*. described treatment options for HIV and HHV8 negative CD, the first-line treatment for UCD was complete surgical resection in 33 out of 43 patients (76.74%), a total of 30 out of these 33 patients achieved complete remission, 3 patients developed recurrence in a new location, 2 of them achieved complete remission after surgical resection. Patients with UCD whom disease was surgically unresectable, treated with radiotherapy [9]. Although the lesion was completely resected in our patient, he continued to have abdominal pain and severe oral ulcers that compromised his oral intake, he was managed with steroids and azathioprine. Fujimoto S., *et al.* analyzed a 142 patients classified into iMCD by using the nationwide Japanese patient registry, treatment was guided by disease severity; patients with mild disease were treated with corticosteroids alone or combined with, tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody and (15%) were followed-up without treatment, while in moderate iMCD patients were treated with TCZ and corticosteroids, in severe cases TCZ, corticosteroids combined with forty-two (89%) iMCD patients with moderate disease were treated with cyclosporine or other immunosuppressive drugs [10].

Pemphigus is one of the common associations with CD. It is considered as a paraneoplastic syndrome and presents as painful oral ulceration with polymorphic skin eruptions. Nikolskaia., *et al.* studied a group of CD patients who presented with lichenoid skin eruptions and stomatitis, the diagnosis of paraneoplastic pemphigus was histopathologically confirmed in 19 out of 28 patients [11]. We had done buccal mucosa biopsy to our patients, histopathology showed sparse chronic inflammatory cell infiltrate inconsistent with paraneoplastic pemphigus.

Many reports have indicated that MCD might overlap or mimic IgG4-related disease; which is a tumor-like enlargement of exocrine glands and/or lymph nodes, histopathology features of the nodal or extranodal tissue are similar to MCD, however an IgG4+/ IgG+ plasma cell ratio of more than 40% is mandatory for the histological diagnosis of IgG4-related disease in addition to high serum IgG4 level in majority of the cases [12,13]. Our patient did not fulfill the immunohistochemical criteria of IgG4-realated disease, his serum IgG4 was within normal range. He needs continuous monitoring for any of IgG4-related disease features, as this disease has different treatment options.

In summary, we have diagnosed a child with CD, although histopathology was consistent with UCD, the clinical phenotype was typically of MCD, he needed a long-term systemic immunosuppressant and steroid treatment. We have extensively worked up the patients looking for a primary cause of CD, or diseases that might mimic CD, this would raise the heterogeneity between UCD and MCD is not clear as has been confirmed in previous studies.

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