Failure to thrive and hypergammaglobulinemia in a 13-year-old girl with Castleman Disease, a case report

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Keywords

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Abstract

Castleman Disease is a rare, lymphoproliferative, non-malignant disorder with two subtypes, unicentric or multicentric, depending on the number of lymph node regions affected. Clinical symptoms may be extremely variable often making the diagnosis difficult or leading to delayed diagnosis. We describe a case of failure to thrive associated with late puberty, and severe hypergammaglobulinemia. Through this case report, we aim to recall the clinical features of this rare disorder and to insist on the importance of a broad differential diagnosis in the presence of failure to thrive especially with abnormal biochemical features.

Introduction

Failure to thrive (FTT) and late puberty are most frequently associated with endocrinopathies, syndromes, anorexia nervosa, inflammatory bowel disease or other chronic conditions. However, as we demonstrate in our case, Castleman Disease (CD), a rare and non-malignant lymphoproliferative disorder with very heterogeneous clinical phenotypes, should also be considered in the differential diagnosis. We describe the case of FTT associated with hypergammaglobulinemia and an inflammatory suprarenal mass.

Case report

We report the case of a 13-year-old girl who presented with FTT associated with late puberty (Figure 1). She has no past medical history and both her parents are healthy. Her birth weight and height were 2740 g and 49 cm, respectively. She has a healthy twin sister who is taller than her (BMI 17,2 kg/m^2, -1 SD). The patient's target height is 170 cm (0,6 SD).

Figure 1:
Body Mass Index curve (Flanders, 2004), red arrow indicates the time of surgery.

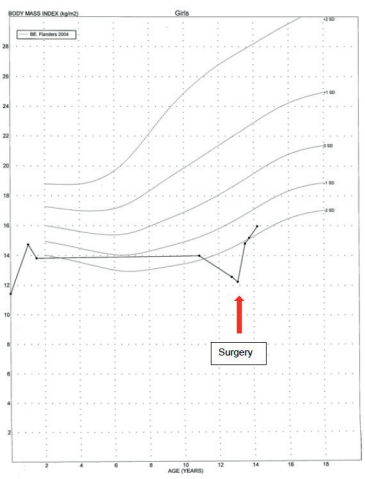
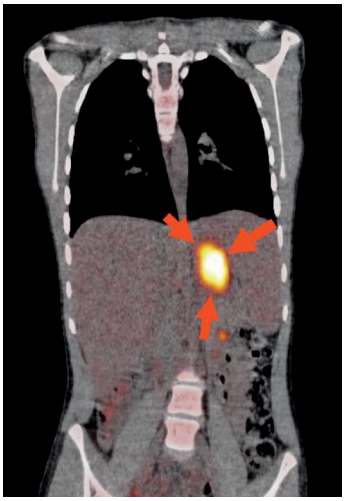


Figure 2:
PET-CT shows a hypermetabolic lesion in the left suprarenal fossa.



In addition to FTT and late puberty, the main symptoms were fatigue, a subfebrile state and a lack of appetite leading to often unfinished meals but frequent snacking. The possibility of anorexia nervosa was excluded based on the absence of food restrictions or the fear of gaining weight. She did not report any digestive symptoms but recalled a blood spot on the toilet paper.

On clinical examination, she was in good condition but lean and pale with a height of 148,8 cm (-1,5 SD); a weight of 27,1 kg (-3,6 SD); BMI of 12,2 kg/m^2 (-4,0 SD) and Tanner stage A1P1M1. She had no dysmorphic features and her vital signs were completely normal.

Complementary investigations revealed an anemia of chronic disease (Hb 7,7 g/dl [N 12-16], hematocrit 27.2% [N 36-46], MCV 63.1 µm3 [N 78-100], reticulocytosis 46.1x103/µl), elevated C-Reactive Protein (CRP 164.4 mg/L [N <5 mg/L]), elevated sedimentation rate (120 mm/h, [N 0-11 mm/h]) normal white blood cell count (7.72x103/µl), elevated platelets (432x103/µl) and normal levels of liver enzymes. Endocrine assessment was normal for prolactin, TSH and free T4, and FSH, LH, estradiol and IGF-1 in the prepubertal range.

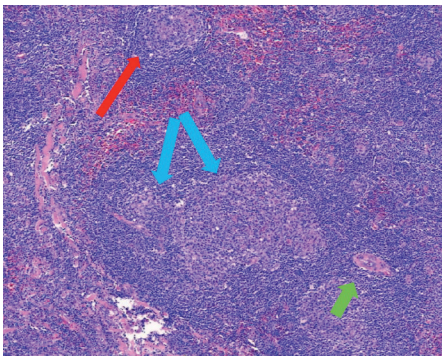
Fecal calprotectin, IgA transglutaminase, anti-Neutrophil cytoplasmic antibodies (ANCA), antisaccharomyces cerevisiae antibodies (ASCA), abdominal ultrasound, gastric endoscopy and colonoscopy were normal.

The following additional workup was performed: tuberculin intradermal test, chest x-ray, lymphocyte typing, and antinuclear factor, all of which were normal. However, a severe hypergammaglobulinemia (total IgG 26,17 g/L [N 5,8-14,5 g/L]) was found.

PET-CT showed a hypermetabolic lesion in the left suprarenal fossa (Figure 2). Transgastric biopsy was performed through echo-

endoscopy. Histologic sections (Figure 3) of the lymph node showed a mainly preserved architecture with hyperplastic lymphoid follicles of various sizes. Some showed slightly atrophic germinal centers surrounded by enlarged mantle cuffs sometimes arranged in concentric rings. Increased vascularity with penetration of radially-oriented hyalinized blood vessels in the germinal centers was also focally observed. Immunohistochemical staining was unremarkable and negative for human herpesvirus-8 disease. The Ebstein-Barr encoding region was negative. There was no evidence of Immunoglobulin heavy chain clonality on molecular analysis. The IgG4/IgG ratio was not elevated and there was no significant amount of IgG4 plasma cells. Folliculolysis and pictures reminiscent of progressive germinal center transformation were also observed. Overall, the histopathologic findings were consistent with a reactive germinal center with Castleman-like modifications.

Figure 3:
Biopsy sample of a suprarenal lymph node, magnification x5, stained with hematoxylin and eosin, shows twinning of the germinal centers (blue arrows), atrophic germinal center with concentric distribution of the mantle cuff (red arrow) and slightly hyalinized vessels penetrating the mantle zone (green arrow).



The suprarenal mass (5,5 cm x 4,5 cm x 3 cm) was surgically resected and the proposed diagnosis of unicentric Castleman Disease was confirmed histologically.. Subsequently, rapid remission ensued with restored appetite, weight gain, and onset of puberty observed. Likewise, biochemical parameters improved rapidly, including normalization of the gamma globulin levels. One year later, there were no signs of recurrence.

Discussion

This case illustrates the need for a stepwise but comprehensive biochemical and imaging workup in the setting of failure to thrive.

We first ruled out the most common diagnoses and then investigated rarer causes. Anorexia nervosa, endocrinopathy and chronic infectious disease were quickly ruled out based on the patient's behavior, endocrine and microbiologic analyses and gastroenterologic workup.

Severe hypergammaglobulinemia (>25g/l) orientated our diagnostic approach. In the largest cohort study of 442 pediatric patients with hypergammaglobulinemia (>20 g/L), Lo et al. reported that 95% of patients had identifiable disorders with nearly half of the patients affected by autoimmune diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease, as well as infectious diseases (EBV, CMV, HIV) and less commonly malignant, drug-related, and other diseases including CD (1).The authors observed that, higher IgG levels, lower white blood cell count, lower hemoglobin levels, lower C-reactive protein levels, as well as female gender were independent risk factors for autoimmune diseases.

Our patient presented with hypergammaglobulinemia and only the low hemoglobin level and the female gender were also in favor of autoimmune / autoinflammatory disease, but extensive workup ruled out such diseases. There was no evidence of chronic infectious disease. Biopsy samples of the suprarenal mass led to the exclusion of malignancy but confirmed reactional lymphoid hyperplasia with Castleman-like modifications.

First described by Benjamin Castleman in 1958, CD is divided into two subtypes depending on the number of affected lymph nodes. Unicentric Castleman Disease (UCD) involves one or more lymph nodes in a single region of the body with similar histopathologic features. UCD is a slowly progressive disease with no specific clinical manifestations (2). Multicentric Castleman Disease (MCD) involves multiple affected lymph node areas, with similar histopathologic characteristics. Patients with MCD present with systemic symptoms and generalized lymphadenopathy, hepatosplenomegaly, cytopenia and organ failure due to inflammatory cytokine secretion (3). In their 2015 study, Munshi et al. estimated the annual incidence of CD in the United States to be between 6500 and 7700 new cases, of which 75% were with UCD, which had a better outcome than patients with MCD (4).

The etiology of CD is unclear. Typical histopathologic aspects of affected lymph nodes are reactive changes, which could be observed with abnormal antigenic stimulation or in a low-grade neoplastic process (5). In the MCD subtype, half of the cases are associated with HHV8 infection, and the other half are HHV8-negative, termed idiopathic MCD (iMCD) (3). Immunological mechanisms such as elevated IL-6 levels are thought to mediate the lymphoproliferative mechanisms. The expression of a viral analog of IL-6 (vIL-6) by HHV-8 may play a role in the downstream mediation of plasmacytosis in the setting of HHV-8 infection (6). Nabel et al. suspected that UCD and or HHV8 negative MCD could be caused by other viruses, but they failed to establish a clear association with any other virus (7). Pediatric CD has similar clinical features compared to adult patients, but the disease mechanism may be different because most adult cases occur in a context of immunodeficiency associated with HIV and/or HHV-8 infection. In children, CD appears to be caused by a primary dysregulation of the immune system (8). In their 2018 retrospective cohort study, Sopfe et al, reported that 75% of their pediatric patients presented with UCD (9). As in our patient, children often present with systemic manifestations such as weight loss, chronic fatigue, fever, and abnormal laboratory results such as elevated erythrocyte sedimentation rate and CRP, microcytic anemia, thrombocytosis and hypergammaglobulinemia (9).

Diagnosis of CD is based on histopathologic findings and is classified into one of two subtypes - hyaline-vascular or mixed/plasmacytic subtype. The histologic differential diagnosis should include malignancies (Hodgkin lymphoma, Non-Hodgkin lymphoma, sarcoma), inflammatory diseases (SLE, systemic-onset juvenile idiopathic arthritis, Sjögren syndrome) or infectious diseases (EBV, CMV, HIV) (5).

The best treatment for UCD is surgery. If complete, surgical resection is usually curative. If surgery is incomplete, radiotherapy or embolization are complementary treatment options. In some cases of limited accessibility, simple clinical surveillance may be considered. Outcomes are excellent with no impact on life expectancy (9).

Although not curative, the management of MCD aims to limit complications due to inflammation and to improve patients' quality of life. In the past, corticosteroids and chemotherapy were used as first line treatments when surgery was not possible. However, their benefits were limited and adverse effects were considerable (8). Currently, new biologic therapies are available including anti-CD20, anti-IL1, and anti-IL6.The current first-line treatment suggested for pediatric patients with MCD is the use of tocilizumab, an anti-IL-6 receptor monoclonal antibody, but recommendations regarding treatment duration and adverse effects are still expected (8, 10).

Conclusion

Castleman Disease is a rare and clinically heterogeneous disorder frequently associated with FTT in children, systemic manifestations, and hypergammaglobulinemia. The diagnostic workup should include autoimmune/autoinflammatory diseases, infectious diseases, malignancies or lymphoproliferative disorders such as CD.

The prognosis of UCD, the most common form of CD in children, is generally excellent after surgical excision with rapid resolution of symptoms. The inflammatory symptoms associated with MCD are alleviated with new biologic therapies that help to improve patients' quality of life.

Conflict of interest

The authors have no conflict of interest to declare.

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