

Genital Involvement in Pre-Pubertal Pediatric Population: a Rare Aspect of Crohn's Disease

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Abstract

Crohn's disease is an inflammatory bowel disease (IBD), characterized by chronic intestinal inflammation that causes the loss of immune tolerance leading to bizarre inflammatory signals and disruption of mucosal barriers. Environmental triggers and interaction of genetic determinants also play an indispensable role. In this case report, we present a pre-pubertal girl with intermittent and refractory genital swelling. We emphasize that Crohn's disease must be considered in the differential diagnosis of recurrent, non-tender, erythematous and edematous lesions of the genital area. We conclude with future directions for diagnosing and managing vulvar Crohn's disease in pediatric population.

Key Words: Crohn's disease (CD), Inflammatory Bowel Disease (IBD), Infliximab, Tumor necrosis factor alpha (TNF- α), Vulvar swelling.

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1- INTRODUCTION

The incidence of pediatric IBD is upsurging, particularly in children younger than 10 years old. IBD affects approximately 2 million Americans, including 80,000–100,000 children, up to 25% of patients present before 18 years of age (1). A systematic review of pediatric-onset IBD demonstrated a global increase in both developing and developed countries during 1950–2009 (2); this ascent was most distinct for Crohn's disease alone. A population-based retrospective cohort study of all children diagnosed from 1994 through 2009 in Ontario, Canada reported an overall hike in the prevalence of pediatric-onset IBD, from 9.4 per 100,000 children in 1994 to 13.2 per 100,000 in 2009 (3). Within the pediatric population (up to age 18 years), a positive family history of IBD is most often found when CD was diagnosed prior to age 11 years (4).

Crohn's disease can affect any part of gastrointestinal tract (5). It can present with signs and symptoms of bowel inflammation with or without the presence of fistulas/abscesses, or as a far off lesion independent from the lesioned bowel. There is a variety of Crohn's disease related extra intestinal clinical demonstrations, which are relatively classical and preeminent and may involve the skin, episcleritis and uveitis, sacroiliitis, ankylosing spondylitis and osteopenia/osteoporosis (6). Crohn's disease related genital involvement is very rare in all age groups. Involvement of gynecological organs is often unrecognized and misdiagnosed (7). Due to the lack of knowledge concerning gynecological aspects of CD, patients are usually not correctly managed and undergo inappropriate treatments (8). Rectovaginal fistulas and ovarian involvement of CD have been extensively described (9, 10), however there are only few series in the literature reporting genital complications

of CD and even less so regarding vulva involvement of CD. Vulvar region cutaneous Crohn's disease on physical examination can present with a variety of manifestations, including labial swelling, erythema, nodules, plaques, pustules/papules and knife-like ulcerations(11,12). Fissures, fistula and sinus tracts, and abscesses may also be noted (12). Extensive scarring with severe deformity may also occur (12). When the diagnosis of vulvar region cutaneous Crohn's disease is unclear, skin biopsy can be performed to confirm the exact diagnosis¹³.

2- CASE REPORT

A 10 year-old African-American girl with Crohn's disease was referred to our outpatient pediatric gastroenterology clinic for consultation regarding a chronic and intermittent labial swelling for longer than 2 years. The patient was diagnosed with perianal and Ileocolonic Crohn's colitis at the age of 6 years. She was treated with anti-tumor necrosis factor drug (infliximab) 5mg/kg every 8 weeks with resolution of gastrointestinal symptoms. The patient was seen by the gynecologist for labial swelling and itching, and was treated with maintenance of good local hygiene, warm sitz baths and topical hydrocortisone. Itching resolved with this treatment regimen, however the vulvar edema persisted which raised the concern for ovarian pathology or adrenal hyperplasia. Serum ehydroepiandrosterone (DHEA), 17 hydroxyprogesterone and testosterone levels were unremarkable. A pelvic ultrasound revealed two hypoechoic circumscribe masses within left adnexa with normal uterine and ovarian anatomy. Metronidazole was then added to treatment, which decreased the swelling for a period of 8 months, but it persisted despite treatment. Based on the provided known medical history of CD, the possibility of undiagnosed cutaneous CD involving vulvar region was raised and

further work-up, including blood tests, upper endoscopy, colonoscopy and MR Enterography (MRE) was pursued. Laboratory evaluation demonstrated normal blood inflammatory markers, including an erythrocyte sedimentation rate (ESR) and a C-reactive protein (CRP) level. The infliximab trough level and Human anti-chimeric antibodies (HACAs) were also found to be non-measurable hence the dose of infliximab was increased to 5mg/kg every 6 weeks. The presence of perianal region skin tags and anal fissuring were noted on physical examination, but they appeared friable and tender to touch. No perianal or rectovaginal fistula was noted. Evaluation of the vulvar region demonstrated a labial enlargement, skin thickening and subcutaneous edema. On the external genital examination the right labia majora was abnormally enlarged and edematous, with mild swelling of labia minor bilaterally (**Figure.1**). To assess her gastrointestinal CD, upper and lower endoscopies were done. Upper endoscopy was normal, but colonoscopy revealed colorectal inflammatory changes. Multiple biopsies were taken from terminal ileum, cecum, and colon through the rectum. Biopsies revealed proctosigmoiditis,

however MRE demonstrated normal rectosigmoid colon bowel wall circumferential thickening with no edema. No active or chronic enteritis was found, but imaging revealed a mild urethral inflammation of unknown etiology. No pelvic free fluid was found. Urine cultures were unremarkable.

The vulva biopsy demonstrated diffuse dermal chronic inflammation and reactive epidermal changes with irregular acanthosis, parakeratosis and a superficial neutrophilic infiltrate of the epidermis associated with diffuse lymphoplasmacytic infiltrate with non-necrotizing granulomas with multinucleated giant cells involving the superficial, mid and deep dermis of vulva region. Based on her clinical and laboratory findings, the dose of Infliximab increased to 7.5mg/kg intravenously every 6 weeks and then to 10 mg/kg every 4 weeks. Interestingly with these changes, no improvement in the vulvar swelling was appreciated and her external genitalia swelling and edema persisted. Most recent EGD and colonoscopy with Ileoscopy revealed normal exam with resolution of previously noted proctosigmoiditis.



Fig.1: Description: Asymmetrical labial edema with erythema, skin erosions, linear ulceration in the interlabial sulci and enlarged clitoral hood.

3- DISCUSSION

Crohn's disease can affect any part of gastrointestinal tract (GI tract). It has a strong hereditary component that has been observed to present in multiple family members. It is also considered to be an autoimmune disease that is responsive to therapy with monoclonal antibodies like infliximab and adalimumab, Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and mercaptopurine and glucocorticoids like prednisone. Intestinal Crohn's disease presents as abdominal pain, diarrhea, blood in stool and weight loss. Extra-intestinal manifestations are often seen in patients with Crohn's disease, which may also involve the vulvar region although, is rare but seen. Pathologically, CD is demonstrated by intestinal transmural inflammation and skips lesions. This transmural nature of the disease can lead to fistulas formation, depending on the regions of involvement, entero-enteric, entero-vesical, entero-vaginal and entero-cutaneous fistulation are some of the common complications.

Histologically, biopsy of the lesions shows granulomatous inflammation characterized by the presence of neutrophils and lymphoid aggregates. The most common finding is a distinct granulomatous inflammation with non-caseating lesions and Langhans type giant cells, but can also present with lymphatic lesions and lesions depicting inflammation and ulcer exudate (14). Vulvar lesions in Crohn's have been linked to rectovaginal fistulae and as metastatic Crohn's in the past. The first line treatment for vulvar Crohn's manifesting as swelling, has been prednisone and metronidazole (14).

Refractory vulvar Crohn's has found to be responding to infliximab (15). Other options for induction include aminosalicylates (mesalamine, sulfasalazine), methotrexate, antibiotics, and biological agents targeting tumor

necrosis factor (TNF), integrin, and Interleukin-2 (IL-2) (16-19).

These therapies may be used instead of or in conjunction with corticosteroids. Although, not recommended for monotherapy for induction of remission, the thiopurine immunomodulators azathioprine and Mercaptopurine (6-MP) may be added to the corticosteroid regimen if needed (17, 19). Maintenance therapy for pediatric CD includes many of the same agents used for induction. In our patient, treatment of vulvar CD was disappointing with metronidazole, corticosteroid and infliximab, so adalimumab with MP initiated with improvement.

4- CONCLUSION

Cutaneous Crohn's disease, including vulvar region involvement, is much often recalcitrant to treatment (20) and there is no unanimity regarding its medical management up to this date (21).

Variable attempts have been observed with topical, intralesional and systemic medical management with a variable success (20-22). Recently, immune system modulators and biologic therapies that target tumor necrosis factor-alpha (TNF- α) have been used successfully to treat some patients with vulvar region Crohn's disease (21, 22) with limited benefit as described in literature. In some treatment-resistant patients with perianal and vulvar region cutaneous Crohn's disease surgical debridement for example, vulvectomy may be indicated (20-22).

Our case describes a pre-pubertal female patient with an established diagnosis of Crohn's disease who was on maintenance therapy with infliximab but still progressed to vulvar region. She had been treated for her intestinal Crohn's disease appropriately as evidenced by her repeated colonoscopy. Development of vulvar lesions after the remission illustrates that it was not metastatic but an extra intestinal

manifestation. Vulvar Crohn's disease in refractory to therapy with corticosteroids, metronidazole, mesalamine and infliximab. We want to bring in attention to all gynecologists, GI specialists and all primary care physicians that any patient with refractory genital lesion with known Crohn's disease could have an extra-intestinal clinical manifestation of cutaneous CD. Its early recognition, confirmation, diagnosis and appropriate treatment can decrease morbidity.

5- CONFLICT OF INTEREST: None.

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