Case Report

Childhood-Onset Eosinophilic Granulomatosis with Polyangiitis with a Vulvar Granuloma: A Case Report and Review of the Literature

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A B S T R A C T

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare multisystem necrotizing vasculitis associated with eosinophilia and extravascular granuloma and classically involving the upper and lower airways. There have only been a few reported cases of gynecologic involvement in EGPA.
Case: We present an 8-year-old girl diagnosed with EGPA with a vulvar granuloma in what is, to our knowledge, the first reported pediatric gynecologic manifestation of EGPA. Interestingly, the vulvar granuloma did not respond to initial immunosuppressant treatment with prednisone and methotrexate and required treatment regimen modification with mycophenolate mofetil resulting in granuloma resolution.
Summary and Conclusion: EGPA in the pediatric population has a relatively high mortality rate compared with in the adult population thus it is important that vulvar granulomas associated with EGPA should be included in the differential diagnosis of a vulvar mass allowing for the prompt diagnosis and treatment of this potentially fatal disease in children.
Key Words: Vulvar lesion, Vulvar mass, Granuloma, Vasculitis, Eosinophilic granulomatosis, Churg-Strauss

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly named Churg–Strauss syndrome, is a rare multisystem necrotizing vasculitis of small and medium-sized vessels associated with eosinophilia and extravascular granulomas classically involving the upper and lower airways.[1] Although EGPA is a rare disease in adults, it is extremely rare in childhood. Because of its rarity, epidemiologic data on pediatric EGPA have not been reported but at present there are approximately 106 pediatric cases of EGPA in the literature.[2–5] From the existing data it is suggested that children with EGPA develop more cardiorespiratory manifestations compared with adults, leading to worse long-term outcomes with a higher mortality rate.[2] There have only been a few reported cases of gynecologic involvement in EGPA.[6–8] Herein we present an 8-year-old girl diagnosed with EGPA with a vulvar granuloma in what is, to our knowledge, the first reported pediatric gynecologic manifestation of EGPA. Although it is a rare and unique manifestation, vulvar granulomas associated with EGPA should be included in the differential diagnosis of a vulvar mass allowing for the prompt diagnosis and swift treatment of this potentially fatal disease in children.

Case

An 8-year-old girl with a history of asthma and allergies presented to her pediatrician at Kaiser Permanente in Sacramento, California, complaining of a painful, swollen left cheek. The pediatrician identified an indurated mass in close proximity to the parotid gland and with concern for an abscess she was admitted to the hospital for intravenous antibiotics and further workup. After minimal improvement with antibiotics, a biopsy was done, which revealed a granulomatous reaction with an eosinophil infiltrate. Unclear of the of the etiology of this granuloma, she received multiple local steroid injections over the course of several months with only minimal improvement in size.

Seven months after the presentation of the parotid granuloma, the patient noticed a vulvar mass. Physical examination showed a firm mass on the left posterior labia majora measuring 4.2 cm × 2.0 cm. It was erythematous, minimally tender, and not warm to touch (Fig. 1). A shave biopsy of the labial mass revealed a noncaseating granuloma with eosinophils. The patient was referred to Pediatric Rheumatology for further investigation. Simultaneous to the vulvar mass development, the patient was found to have multiple pulmonary nodules and hilar adenopathy. Laboratory testing revealed eosinophilia and antineutrophil cytoplasmic antibodies negativity. An axillary mass was also found and identified as a granuloma. Because of these findings of multiple granulomas, in addition to her history of asthma and allergies, the rheumatologist diagnosed EGPA and initiated systemic steroid therapy. Prednisone 30 mg daily treatment was started. After 2 weeks of prednisone

The authors indicate no conflicts of interest.

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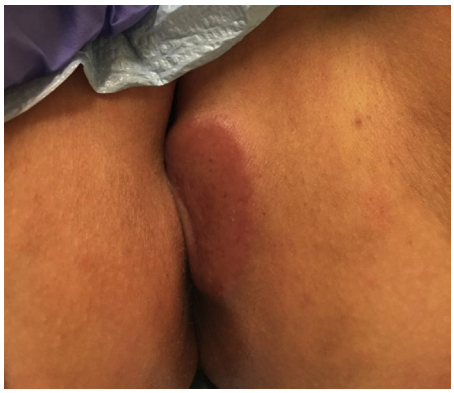

Fig. 1. A firm mass, which was erythematous, minimally tender, and not warm to touch on the left posterior labia majora measuring 4.2 cm × 2.0 cm.

treatment, the lung lesions as well as the parotid, axillary, and labial granulomas decreased in size, but did not resolve. Because there was persistence and because of the irritative nature of the vulvar granuloma, it was decided to pursue a more aggressive treatment regimen. Thus methotrexate treatment was started. Methotrexate is one of the commonly recommended steroid-sparing medications used in moderate-severity EGPA although there have been no trials in children for EGPA.[9] Weekly subcutaneous treatment with methotrexate 25 mg was started and the patient was instructed to continue the prednisone for 3 months and finish with a gradual taper. At this time, the granulomas had almost entirely resolved.

However, 4 months after initiation of methotrexate treatment, the patient began to notice some vaginal bleeding as well as new vulvar irritation. On examination, the left labial mass grew larger and extended into the inner vaginal wall. Because this mass was the only remaining active clinical manifestation of EGPA, the patient was referred to Pediatric Gynecology for further evaluation and to confirm that it was a granuloma and not due to another cause. On gynecologic exam, 2 separate vulvar masses were identified, a 3.0-cm circular mass in the left labia majora and a 1.0-cm mass located inferiorly (Fig. 2). A vaginal endoscopy and two 3-mm punch biopsies using anesthesia were performed. The specimens were sent to Stanford University Medical Center Department of Pathology for

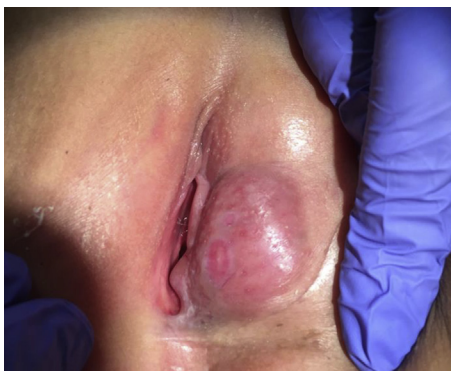

Fig. 2. Two separate vulvar masses; a 3.0-cm circular mass in the left labia majora and a 1.0-cm mass located inferiorly.

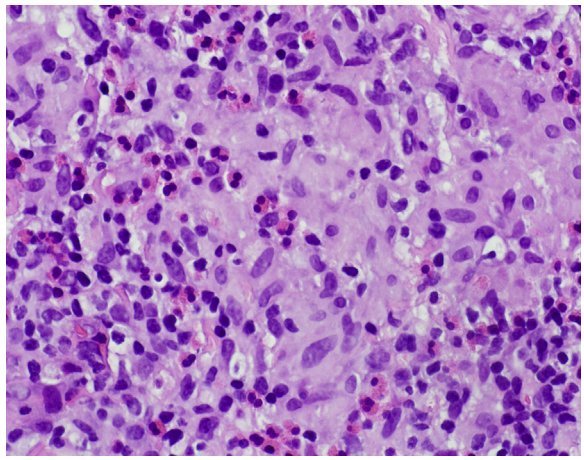

Fig. 3. A non-necrotizing granulomatous inflammation with varying quantities of eosinophils.

external consultation and were confirmed to be a non-necrotizing granulomatous inflammation with varying quantities of eosinophils (Fig. 3). Over the next 2 months, the vulvar granulomas increased in size with the 2 granulomas contiguous with each other. At this time, the granuloma measured 5.0 cm × 3.4 cm and progressed in size, clearly unresponsive to the systemic methotrexate treatment. Because of the lack of response, a local steroid injection directly into the granuloma was trialed. Two cubic centimeters of triamcinolone acetonide 40 mg/mL with 1% lidocaine (10 mg/mL) was injected into the granuloma. At follow-up 1 month later, the granuloma appeared to be stable, but softer (Fig. 4). Because of the lack of resolution and ongoing discomfort due to the mass, her methotrexate dosage was increased to 30 mg weekly. Despite the increase in dose, the granuloma continued to grow, causing the patient significant discomfort (Fig. 5). After 2 months of treatment with the higher dose of methotrexate and progression of the granuloma, the pediatric gynecologist decided to supplement with topical steroids, which have been shown to show improvement in vulvar granulomas associated with sarcoidosis.[10] Topical clobetasol was used twice a day for 6 weeks, which resulted in minimal improvement. Because of the persistent and symptomatic vulvar granuloma, a new systemic immunosuppressive, steroid-sparing medication was initiated. The patient was given mycophenolate mofetil 500 mg every morning and 250 mg every evening, which has been previously documented for use in pediatric EGPA cases.[4,9] With no adverse effects, this was increased to 750 mg twice a day. Within a month, the granuloma decreased significantly in size. At present, the patient has been receiving mycophenolate mofetil for 6 months and the vulvar granuloma has largely disappeared with only some residual granulomatous tissue appreciated on exam, although importantly no new granulomas have formed.

Summary and Conclusion

EGPA with gynecologic involvement is extremely rare and to our knowledge, this is the first reported case in a pediatric

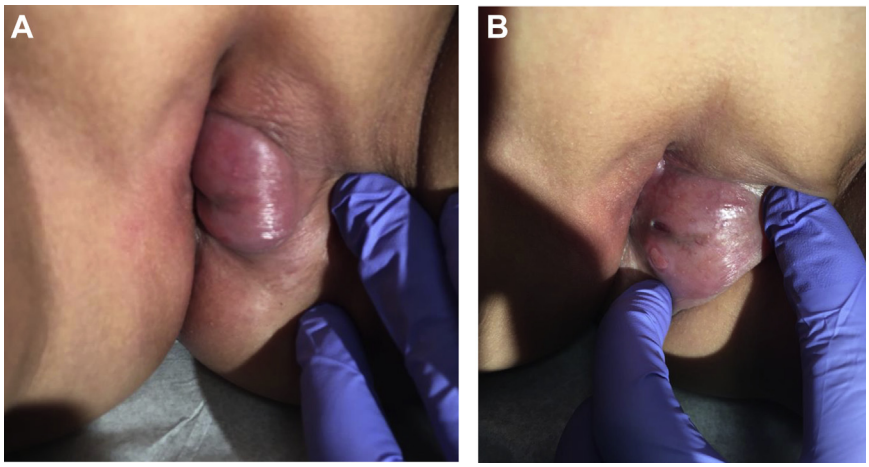

Fig. 4. (A) Left labial granuloma; (B) Left labial granuloma with central portion demonstrating prior biopsy site.

patient. Our patient had previous presentations of disease before the onset of the vulvar granuloma, including a parotid granuloma with eosinophils, which enabled a more directed diagnostic approach to the vulvar mass. However, it is possible for a pediatric patient with EGPA to initially present with a vulvar granuloma. Including EGPA in the differential diagnosis for a vulvar mass, as well as understanding the diagnostic workup and various treatment options, is warranted for this potentially fatal disease in children.

The differential diagnosis for a pediatric vulvar mass includes a gonadal remnant, hernia, Bartholin duct cyst, abscess, benign tumors such as rhabdomyoma, lipoma, fibroma, granular cell tumor, neurofibromatosis, hemangioma, and childhood asymmetry labium majus enlargement.[11] Malignant tumors include sarcoma botryoides or an endodermal sinus tumor.[11] Because of the possibility of EGPA presenting with a vulvar mass, it is important to consider it in the differential diagnosis as well.

The most commonly used classification criteria for diagnosis of EGPA is from the American College of Rheumatology, although these criteria were formulated on the basis of adult data.[12] The American College of Rheumatology supports a diagnosis of EGPA if 4 of the following 6 criteria are met: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils.[1] Biopsies for histological identification of eosinophils, granulomas, and/or vasculitis are not required for diagnosis but provide confirmation.[12] The clinical presentation of pediatric EGPA is known to vary, with the involvement of numerous organ systems, although pulmonary involvement is typically always present. In a study of the largest pediatric EGPA data cohort to date, 14/14 (100%) of the patients had pulmonary manifestations and 12/14 (86%) specifically had asthma.[2] Although EGPA is a necrotizing vasculitis, only 2/12 (17%) of the patients in the cohort had histopathologic evidence of vasculitis.[2] The most likely reason for this finding is that vasculitis is thought to be in the later stages of the disease, and that many of the pediatric patients diagnosed with EGPA were identified in the earlier stages of disease. In our case, the vulvar granuloma was likely part of the early presentation of the disease, and with early initiation of systemic treatment, vasculitis has not manifested.

In a review of the literature on prepubertal vulvar masses, most case reports describe performing a diagnostic surgical excisional biopsy of the mass if there is high suspicion that the mass is benign on the basis of history and ultrasound imaging.[11,13] In the case of EGPA, surgical excision of granulomas is not recommended because there is a high likelihood for recurrence. In addition, there are significant surgical consequences from vulvar surgery on a pediatric patient including scarring, asymmetry, and loss of sensation. Instead, we recommend initial punch biopsy of the lesion, regardless of level of suspicion for EGPA.

Prompt initiation of treatment for EGPA is important in preventing progression of disease. The pediatric data on EGPA treatment is lacking but the general approach to treatment begins with high-dose glucocorticoids for 3-6 months.[14] After initial treatment with steroids, remission induction immunosuppressant medications can be used in addition depending on severity of symptoms. For moderate-severity disease, methotrexate, azathioprine, and mycophenolate mofetil have all been shown to be successful in inducing remission in children. In cases of severe disease typically with cardiac, renal, and/or gastrointestinal involvement, aggressive treatment with agents such as

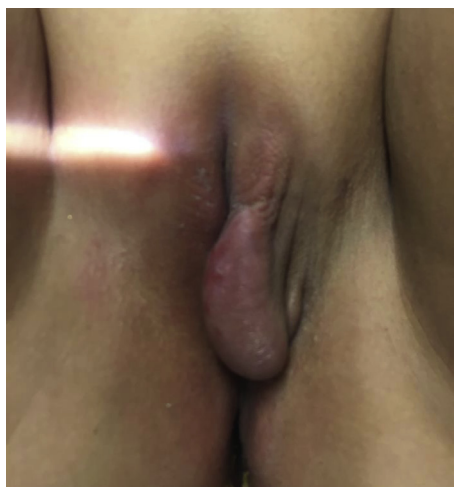

Fig. 5. The granuloma continued to grow, causing the patient significant discomfort.

cyclophosphamide and/or rituximab with or without plasmapheresis can be required.[9] In our case, it was puzzling that the vulvar granuloma did not respond to the methotrexate whereas the other granulomas and pulmonary nodules did. The vulvar granuloma initially responded to prednisone; however, with the methotrexate therapy she experienced growth of the granuloma instead of improvement. A local steroid injection did not result in significant improvement either. In a case report on vulvar granulomas associated with sarcoidosis and in a case of cutaneous granuloma in a pediatric patient, use of high-strength topical steroid cream showed efficacy.[10,15] However, this patient was unresponsive to topical clobetasol. Fortunately, switching from methotrexate to mycophenolate mofetil has worked well in shrinking the vulvar granuloma. Her vulvar granuloma is now nearly resolved and there are no new granulomas. There were some concerns regarding compliance with her medication and transfer of her health care to a different city. However, she continues to do very well with mycophenolate mofetil treatment, and continues every 3 months surveillance in Pediatric Rheumatology and every 6 months in Pediatric Gynecology.

EGPA is a chronic vasculitis and many patients have a relapsing/remitting course. According to one adult study with a mean follow-up time of approximately 50 months, vasculitis relapse occurred in 97 patients (25.3%), whereas 72 additional patients (18.8%) experienced asthma flares, sinusitis, and/or increased eosinophilia, justifying adjustments to therapy.[16] Studies are limited in determining relapse and long-term follow-up. There is even more limited information about disease course and prognosis in pediatric patients in whom this rare vasculitis is even more uncommon. A 2013 literature review of 47 pediatric patients with EGPA determined a mortality of 13% in their patient population.[4] Mortality in adult and pediatric studies were most commonly secondary to cardiac involvement.

Cardiac manifestations are proportionally seen more frequently in pediatric EGPA patients and cardiac involvement is the leading cause of EGPA patient deaths.[17] Our patient underwent a cardiac workup for chest pain with physical activity just before her granulomas presenting, for which her electrocardiogram was abnormal, but her echocardiography was normal. She also has a paternal family history of cardiomyopathy, so she was also referred to the Genetics department and was found to have negative evaluation for risks greater than baseline. Pediatric Cardiology will continue her surveillance annually and as needed for symptoms.

There are currently no official set of society guidelines regarding long-term monitoring for patients with EGPA, including cardiac evaluation or monitoring in patients without cardiac symptoms. A set of recommendations were published in 2015 as a result of a European group consensus meeting. They proposed recommendations for regular evaluation, but they did not specify how to evaluate, how often to evaluate, or via which specific cardiac modality. Additionally, the associated level of evidence was noted as nonapplicable.[17] The American College of Rheumatology is currently working on developing guidelines for antineutrophil cytoplasmic antibodies vasculitis, for which certain aspects might be applicable to patients, specifically children, with EGPA. Because of the paucity of data on EGPA in children, the most effective treatment and ongoing surveillance is yet to be determined.

Understanding that EGPA can present in a variety of different organ systems in children, including gynecologic presentations such as a vulvar mass, is of critical importance in the diagnosis and subsequent care of these unique patients. Once diagnosed, collaboration with a multidisciplinary team, including Rheumatology, Pulmonology, Cardiology and Pediatric Gynecology is essential to the short and long-term care of these complex young patients.

References

1. Jennette JC, Falk RJ, Bacon PA, et al: 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65:1
2. Fina A, Dubus JC, Tran A, et al: Eosinophilic granulomatosis with polyangiitis in children: Data from the French RespiRare cohort. Pediatr Pulmonol 2018; 53: 1640
3. Yener GO, Tekin ZE, Demirkan, et al: Eosinophilic granulomatosis with polyangiitis without respiratory symptoms or asthma in an adolescent: case report and literature review. Rheumatol Int 2018; 38:697
4. Gendelman S, Zeft A, Spalding SJ: Childhood-onset eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome): a contemporary single-center cohort. J Rheumatol 2013; 40:929
5. Zwerina J, Eger G, Englbrecht M, et al: Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum 2009; 39:108
6. Famokunwa B, Ockrim J, Manson JJ: Eosinophilic granulomatosis with polyangiitis presenting with a vesicovaginal fistula. Rheumatology (Oxford) 2017; 56:1080
7. Sukhdeo A, Bertouch J: Gynecological involvement in eosinophilic granulomatosis with polyangiitis. Int J Rheum Dis 2016; 19:932
8. von Maltzahn M, Kinloch M, Truchan M, et al: Vasculitic adnexal involvement in eosinophilic granulomatosis with polyangiitis (Churg-Strauss angiitis). J Clin Rheumatol 2014; 20:341
9. Morishita KA, Moorthy LN, Lubieniecka JM, et al: Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2017; 69:1470
10. Vera C, Funaro D, Bouffard D: Vulvar sarcoidosis: case report and review of the literature. J Cutan Med Surg 2013; 17:287
11. Lowry DL, Guido RS: The vulvar mass in the prepubertal child. J Pediatr Adolesc Gynecol 2000; 13:75
12. Mouthon L, Dunogue B, Guillevin L: Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). J Autoimmun 2014; 48-49:99
13. Goldrat O, Lingier P, Massez A, et al: Prepubertal vulvar fibroma: neoplasm or physiological condition? J Pediatr Adolesc Gynecol 2016; 29:e67
14. Caltroni M, Oliva E, Gianfreda D, et al: ANCA-associated vasculitis in childhood: recent advances. Ital J Pediatr 2017; 43:46
15. Fisher K, Smith S, Skinner R, et al: Cutaneous Churg-Strauss granuloma in a child. J Cutan Pathol 2009; 36:910
16. Comarmond C, Pagnoux C, Khellaf M, et al: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term follow-up of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013; 65:270
17. Groh M, Pagnoux C, Baldini C, et al: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015; 26:545