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A pediatric case of xanthogranulomatous pyelonephritis in the setting of Covid-19 and multi-system inflammatory syndrome (MIS-C)

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ABSTRACT

Xanthogranulmatous pyelonephritis is a rare, chronic inflammatory pathology of the kidney. It most commonly arises in middle-aged females, but there are case reports and series described in the pediatric population. Here, we discuss the case of a 14 year old male who presented with xanthogranulomatous pyelonephritis in the setting of Covid-19 and multi-system inflammatory syndrome (MIS-C). As xanthogranulomatous pyelonephritis often mimics other diseases that are more prevalent in the pediatric population, our case was only definitively diagnosed with histopathology after surgical resection. This report is novel in that, to our knowledge, it is the first to describe xanthogranulomatous pyelonephritis in the setting of MIS-C.

1. Introduction

Xanthogranulomatous pyelonephritis (XGP) is a chronic inflammatory pathology of the kidney that presents as pyelonephritis with associated granulomatous inflammation and foamy lipid laden macrophages, or xanthoma cells, of the renal parenchyma [1]. It most commonly affects middle aged women, and typically presents in the setting of large obstructing renal calculi in both adults and children [1,3,4]. XGP has been documented in approximately 16% of pediatric nephrectomy specimens [5–9].

There are two main variants of XGP: diffuse XGP, which is seen in about 75–90% of all cases, and focal XGP, which is more commonly observed in children [9–11]. The diffuse form involves the entire kidney while the focal form is isolated to a single segment or pole; most commonly the lower pole [12]. Focal XGP has also been termed "pseudo-tumoral" as it often mimics renal tumors (eg, Wilms tumor, clear cell carcinoma), and histopathology is necessary to obtain an accurate diagnosis [9,13].

There are several case reports and case series documenting XGP in children, but upon literature review, there are no published data regarding XGP in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), also known as Covid-19 infection, or in the setting of multi-system inflammatory syndrome in children (MIS-C) following Covid-19 infection. We describe a case of a 14 year old male who developed XGP after Covid-19/MIS-C. We also review the current literature regarding XGP in children including typical presentation, evaluation, imaging modalities, complications, and management.

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2. Case report

The patient is a 14 year old male who initially presented to the emergency department (ED) with six days of fevers, reportedly 104.8 °F at home, with a concomitant erythematous macular rash, fatigue, and abdominal pain. He had a positive FaStep COVID-19 antibody test at his primary care provider's office earlier that day. He was admitted with concern for MIS-C. Labs on admission were notable for a negative COVID-19 PCR, negative viral respiratory panel, negative urinalysis, fibrinogen 897 mg/dL, ferritin 347.6 ng/mL, erythrocyte sedimentation rate (ESR) 85 mm/h, C-reactive protein (CRP) 21.36 mg/dL, and white blood cell count (WBC) 10.67 10^3/μL. Rheumatology was consulted for MIS-C management and he was treated according to the Children's Hospital of Philadelphia MIS-C clinical pathway protocol [14] with intravenous (IV) immunoglobulin 95mg, aspirin 81mg, IV methylprednisolone 47mg twice daily which was transitioned to oral prednisone and tapered daily for four days from 40 mg to 10 mg, and a proton pump inhibitor, with plans for outpatient follow up with rheumatology. He returned to the ED 6 days later with persistent fever, emesis, and right hip pain. After testing positive for metapneumovirus, he was discharged. Two weeks later, he again presented to the ED, endorsing persistent fevers, abdominal pain, emesis, and a new weight loss of 5–10 pounds. A computed tomography (CT) of the abdomen and pelvis was obtained which demonstrated an 8.7 × 6.5 × 5.1 cm enhancing mass within the septa of the right kidney obliterating the posterior renal fat and perinephric space with invasion of the nearby muscle and prominent lymphadenopathy along the right renal artery (Fig. 1A and B). These imaging findings were concerning for a renal neoplasm. Therefore, the child subsequently underwent a right radical nephroureterectomy (Fig. 1C) with pericaval and periaortic lymph node dissection. His intra- and post-operative courses were uncomplicated. Pathology was consistent with XGP as demonstrated by the presence of a prominent mixed inflammatory infiltrate (Fig. 1D and E) with numerous aggregates of foamy histiocytes highlighted by CD68 and CD163 staining (Fig. 1F and G).

3. Discussion

3.1. Epidemiology

XGP is an uncommon diagnosis in children [3]. Though first described in 1916 by Schlagenhaufen [15], it was not reported in the pediatric literature until 1963 when Avnet et al. and Friedenberg and Spjut each published case reports [16,17]. To date, less than 300 cases have been described in the pediatric literature [18–20] with the largest case series documented in Ireland from 1963 to 2016 which included 66 children ranging from 1 to 14 years of age [21]. The reported age of onset varies widely from 21 days to 16 years, with 60–75% of cases being diagnosed before 5 years of age [12], and it appears to affect both genders equally [22]. Overall, XGP is more commonly described in the left kidney [23–25], but our patient had right-sided disease. Bilateral disease is rarely seen, with only a total of sixteen reports in the literature [12,19,26].

Congenital anomalies including vesico-ureteral reflux, uteropelvic junction obstruction, horseshoe kidney, neurogenic bladder, caliceal diverticulum, diverticular bladder, and bladder exstrophy have been linked with XGP which may likely be attributed to chronic urinary tract infections that are often found with these anomalies [27–30]. The bacteria most commonly associated with XGP are those that cause urinary tract infections including *Proteus* spp., *Escherichia coli*, *Pseudomonas* spp., and *Klebisiella* [6,12] as well as less common strains such as *Actinomyces* spp., *Streptococcus faecalis* and *methicillin resistant Staphylococcus aureus* [31–33]. The inflammation generated from infection appears to be more critical for the development of XGP than the speciation of the bacteria [6,

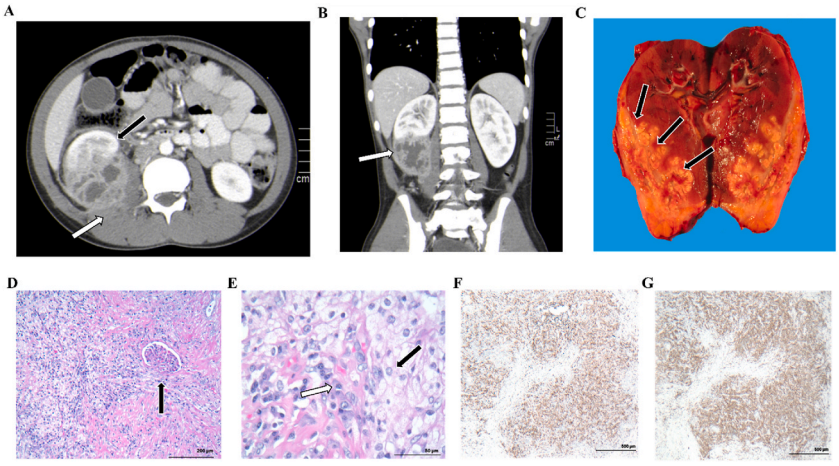

Fig. 1. A: Computed tomography (CT) cross-sectional, axial view of right renal mass (black arrow). Mass appeared to extend into psoas muscle with associated inflammatory changes in the area (white arrow). B: CT coronal view of right renal mass (white arrow). C: Gross pathologic specimen demonstrating lobules of infiltrating fibrosis in lower pole of cross-sectioned right kidney (black arrows). D: Photomicrograph (10 ×) of histology specimen demonstrating fibrosis surrounding a renal glomerulus (black arrow) with associated surrounding plasma cells and macrophages. Scale bar represents 200 μm. E: Photomicrograph (40 ×) of renal parenchyma fibrosis. Black arrow indicates foamy lipid laden macrophage. White arrow indicates plasma cell. Scale bar represents 50 μm. F: Photomicrograph (10 ×) of CD68 immunostaining (brown color) of macrophages infiltrating kidney. Scale bar represents 500 μm. G: Photomicrograph (10 ×) of CD163 staining (brown color) of macrophages infiltrating kidney. Scale bar represents 500 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

19]. Urinary obstruction secondary to renal calculi was present in 38–83% of reported cases of XGP [25,34,35], with nearly half of those calculi considered staghorn [10,36]. Although most cases of XGP in children were attributed to some pathologic process inducing chronic inflammation, other etiologies described include lymphatic obstruction, arterial or venous insufficiency, disturbances in lipid metabolism, or impaired leukocyte function [4,37,38].

3.2. Presentation and initial evaluation

The onset of XGP is usually subacute and resembles that of chronic pyelonephritis. Symptoms are typically nonspecific and range from abdominal/flank pain, fever of unknown origin, malaise, palpable flank or abdominal mass, and weight loss; many of which were described in the current case [39–41]. In children, these symptoms may also lead to concomitant growth retardation [42]. Laboratory findings may show microcytic anemia, elevated ESR, elevated CRP, leukocytosis, or thrombocytosis; findings consistent with chronic inflammation [10]. Urinalysis results vary and may include signs of chronic pyelonephritis with pyuria seen in 90% of specimens, but, hematuria or proteinuria may also be present [20]. In the current case, the urinalysis was normal on multiple occasions, but the patient's other presenting features were consistent with a chronic inflammatory state. Since this patient did not have renal calculi, we presume that the source of his XGP may have been related to the chronic inflammatory state associated with MIS-C following Covid-19 infection.

The diagnosis of XGP may be challenging based on presenting symptoms, physical exam findings, and laboratory results. Though not definitive, imaging is useful in making the diagnosis and helping to guide management. Contrasted CT scans are the most frequently used imaging modality and unilateral renal inflammation and enlargement are the most consistent findings [43]. In the diffuse type of XGP, distortion of renal parenchyma and renal pelvis may be noted. In the focal form, a localized intrarenal mass with fluid-like attenuation may be seen [28]. The most commonly described radiologic appearance is the "bear paw" sign, which is due to the presence of multiple, hypoechoic areas of the dilated collecting system with pus and debris that is surrounded by an enhanced rim of contrast medium [28,43,44]. An important distinction to note is the difference between "bear paw" sign seen in XGP and the "claw" sign which has been described in Wilms tumor and refers to a normal rim of renal parenchyma surrounding an inner renal mass [45].

Renal ultrasonography (US) may also help differentiate between focal and diffuse XGP, which is important since management may differ between types. US demonstrates renal enlargement with multiple hypoechoic areas in diffuse XGP and a localized hypoechoic mass in the focal subtype [28,46–51]. Magnetic resonance imaging (MRI) is an option in patients who are unable to tolerate CT contrast. On T1-weighted imaging, the fibrosis of the lesion is isointense to the renal parenchyma and has a low-signal intensity on T2-weighted imaging similar to that of normal renal parenchyma [12]. The MRI findings vary based on the amount of xanthoma cells present which affects the intensity detected and may be more useful in characterizing the focal form from a malignancy [12,52].

Finally, because XGP presents in children as an abdominal mass, it is sometimes mistaken for other pediatric tumors, such as Wilms tumor, renal cell carcinoma, neuroblastoma, leukemia, or lymphoma [13,22,28,53,54], inflammatory processes including pyelonephritis, actinomycosis, renal tuberculosis [12], and renal abscesses [28]. Therefore, the diagnosis requires histology. The defining histologic findings are lipid-laden foam cell macrophages or xanthoma cells [15]. In the current case, CD68 and CD163 staining were utilized to highlight these macrophages and help further confirm the diagnosis. CD68 is a pan-macrophage marker [55] while CD163 is a marker of M2 macrophages, which are involved in chronic inflammation [56] and thus lend support to the diagnosis of XGP.

3.3. Complications

An array of complications of XGP have been described which are often secondary to involvement of adjacent organs. In children, these complications include abscesses involving the psoas muscle [57–59] or perinephric spaces, fistulas including nephrocutaneous [60,61], nephroduodenal [62], nephrocolonic [25,61,63] and even nephrobronchial [64]. There have also been reports of concomitant liver lesions [65], bronchiectasis [66] and associated renal vein thrombosis [67].

3.4. Management

The mainstay of therapy for XGP is surgical resection with total nephrectomy for the diffuse form and partial nephrectomy for the focal form [19]. Both transperitoneal and extraperitoneal open surgical approaches have been successfully described in pediatric patients [48,68]. Data driving the decision to use an open versus minimally invasive approach to resection are not clear. Studies in the adult population show no difference between approaches [69], but data are limited in the pediatric population. Joshi et al. published the first case series of three patients aged 15 months to 9 years and reported laparoscopic retroperitoneal nephrectomy to be a safe option [70]. Additional reports of laparoscopic nephrectomy for children with XGP have been documented [30,71–74]. Drainage of extrarenal abscesses prior to definitive surgical therapy may be used to reduce acute inflammation and potentially create a cleaner surgical field for nephrectomy as an attempt to mitigate post-surgical complications [36,77–80]. Biopsy prior to nephrectomy is generally avoided in the United States, based on the concern for Wilms tumor and the risk of upstaging in that setting [81].

Debate exists regarding medical management of XGP due to potential for malignancy [21]. A few case reports describe non-operative medical management of XGP with antibiotics alone [9,82,83]; though there are also reports of patients proceeding to nephrectomy after failure of medical management [80]. Upasani and colleagues reported a case of a 17 year old male with XGP who underwent embolization of the renal artery to devascularize the involved renal parenchyma and ablate the infected portion to avoid repeat surgery after initial attempts at nephrectomy failed [7]. In our patient, the concern for malignancy based on imaging findings showing muscle invasion and prominent lymphadenopathy along the right renal artery led to the decision to proceed with surgical extirpation.

4. Conclusion

To our knowledge, XGP in children in the setting of Covid-19 and MIS-C has not yet been reported. XGP usually presents in adults who have chronic pyelonephritis secondary to nephrolithiasis, making the current case unusual. The presentation of XGP may mimic other more common renal pathologies rendering it difficult to establish the correct diagnosis without histopathology.

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Consent

Consent to publish the case report was not obtained. The University of Alabama at Birmingham Institutional Review Committee deemed the study exempt.

Author contributions

Julson, Noor, and Williams were involved in literature review and manuscript preparation. Wicker analyzed pathological specimens. Beierle provided senior guidance with manuscript preparation. All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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