Pediatric Nephrology (2023) 38:1041–1044
https://doi.org/10.1007/s00467-022-05666-3

CLINICAL QUIZ

An extremely rare cause of flank pain: Answers

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Received: 22 May 2022 / Revised: 7 June 2022 / Accepted: 8 June 2022 / Published online: 24 June 2022

Keywords Child · Renal infarct · Kidney infarct · COVID-19 · COVID-19-associated coagulopathy

Answers

1. *What is your most likely diagnosis?*

   The multifocal bilateral wedge-shaped image (triangular defects in the renal parenchyma) is typical for renal infarction and allowed us to diagnose the patient with renal infarction. In addition to the wedge-shaped image, the presence of nausea/vomiting, flank pain, high C-reactive protein, and D-dimer values also indicate acute kidney infarction.

2. *What is the differential diagnosis in this child?*

   Although renal infarction can be idiopathic, it is often secondary to an underlying disease [1]. Embolism secondary to cardiac disease is among the leading causes in the adult age group [2, 3]. Trauma, spontaneous renal artery dissection, fibromuscular dysplasia, and thrombotic aneurysms of the renal artery are the causes of renal infarction secondary to renal artery injury [1]. In addition to diseases that may predispose to hypercoagulable conditions, such as hereditary thrombophilic diseases and nephrotic syndrome, renal infarction has also been reported in the course of rheumatological diseases such as systemic lupus erythematosus (SLE), primary antiphospholipid syndrome, polyarteritis nodosa, mixed connective tissue disease, Henoch–Schönlein vasculitis, and Behcet disease [3–5]. Finally, with the COVID-19 pandemic, cases of thrombotic microangiopathy and renal infarction with/without arterial thrombus in the renal vasculature have also been described [6].

3. *What further investigations would you do to confirm the etiology/cause?*

   First, cardioembolic origin, which is the most common cause in etiology, must be ruled out [2]. This healthy-looking 12-year-old patient had no known heart disease. A normal 2D echocardiogram and electrocardiography of the patient excluded possible embolism secondary to cardiac diseases. Renal injury is also one of the common causes of renal infarction along with cardiac causes [1]. The patient had no history of trauma. Angiographic imaging of the arterial tree was performed to exclude the presence of renal injury secondary to diseases such as aneurisms or dissections. Computerized tomography (CT) angiography revealed no thrombus in the abdominal aorta and its branches, as well as in the renal arteries. There was no family history of bleeding or coagulation disorders, and the coagulation profile was normal. However, due to the presence of prothrombotic factors in the etiology of renal infarction, thrombosis tests (Factor V, Antithrombin III, protein C, and S deficiency) were studied to exclude hypercoagulable states [3, 5]. Hemoglobin electrophoresis studied in the differential diagnosis of sickle cell anemia was normal. Complement levels (serum C3 1.2 g/l, serum C4 0.3 g/l) were in normal range. Antiphospholipid and anticardiolipin IgM and IgG antibody titers were negative. Negative ANA (anti-nuclear antibody) and the ENA (extractable nuclear antigen) panel led us to exclude rheumatological diseases such as SLE and mixed connective tissue disease [3, 5].

This refers to the article that can be found at http://dx.doi.org/10.1007/s00467-022-05662-7.

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The patient's history revealed that he and his family members had fever and cough for 3 weeks, but were not tested. COVID-19 PCR and antibodies were sent due to the conjunctival hyperemia of the patient with high fever before hospitalization, as well as lymphopenia and an increase in liver enzymes. Tests were negative for COVID-19 infection on reverse transcription-polymerase chain reaction (PCR) of nasal swab and positive for IgG and IgM antibodies. Renal infarction due to acute COVID-19-associated coagulopathy (CAC) was considered with the present findings in the patient. However, we could not rule out the suspicion of multisystem inflammatory syndrome in children (MIS-C), according to the World Health Organization (WHO) criteria in the patient with the presence of positive serology and laboratory findings accompanied by non-purulent bilateral conjunctivitis developed 3 weeks after the acute infection [7].

4. *How would you manage this child?*

Intravenous antibiotic treatment was initiated in an external center with the suspicion of acute pyelonephritis empirically. Low molecular weight heparin (LMWH) 100 U/dose per kg was added with the diagnosis of acute renal infarction as an anticoagulant therapy. Although renal infarction due to CAC was considered, intravenous immunoglobulin (1 g/kg) therapy and methylprednisolone (2 mg/kg) were given because of ongoing fever and the diagnosis of atypical MIS-C could not be excluded. Echocardiogram revealed patent foramen ovale. The patient, whose fever regressed, lymphopenia and kidney functions improved, and proteinuria resolved (urine beta 2 microglobulin (0.21 mg/l)), was discharged on the 10th day of hospitalization. Since no signs of renal infarction were found in the abdominal CT performed in the first month of treatment, LMWH treatment was discontinued, and the patient was commenced on 3 months of acetylsalicylic acid therapy.

Discussion

In the period after the novel coronavirus disease 2019 (COVID-19) was identified in November 2019 and became a worldwide pandemic, multisystem involvement of the disease was described in many publications [8, 9]. Hematuria, proteinuria, uremia, and increased creatinine were reported as renal involvement of COVID-19 in the pediatric population. Acute kidney injury was also mentioned as a common complication, especially in hospitalized patients [10, 11]. As the pathogenesis of COVID-19-associated coagulopathy and endotheliopathy has been revealed, thromboembolic events have also been reported [12]. However, COVID-19-associated renal infarction is limited to case reports with a small number of adult cases [5, 13–18, 20–23]. These cases are summarized in Table 1. Only one pediatric renal infarction case, thought to be associated with MIS-C, has been reported so far. This case, which was thought to be MIS-C in the foreground with its clinical findings, was reported to be evaluated as idiopathic renal infarct, since no evidence of COVID-19 could be found [19]. To the best of our knowledge, our patient is the first reported pediatric case of renal infarction associated with CAC.

Various complications have been described in respiratory virus infections, including COVID-19. The increased tendency of coagulopathy in COVID-19 patients is one of the important factors that cause morbidity and mortality [24, 25]. The coagulation cascade is triggered by generating a systemic inflammatory response in response to infection. Following this situation, the coagulation system is also activated, and this is called thromboinflammation or immunothrombosis [12]. The pathogenesis of CAC is incompletely understood, but findings suggest that the causes predisposing to thrombosis are hypercoagulopathy, inflammation, cytokine release, endothelial damage, and hypoxia [12, 24, 25]. CAC is typically characterized by severely elevated D-dimer, mildly decreased platelet count, elevated fibrinogen, and slightly prolonged prothrombin time. The most important difference between CAC and disseminated intravascular coagulation (DIC) is the severe reduction of fibrinogen and platelet count in DIC [26]. While venous thromboembolism is most common in CAC, arterial ischemic conditions (extremity, cerebral, coronary, and visceral arteries) can also be seen, as in this case [27, 28].

Conclusion

Renal infarction occurs when blood flow in the renal artery is suddenly interrupted. Wedge-shaped image, nausea/vomiting, flank pain, high C-reactive protein, and D-dimer values indicate acute kidney infarction. In addition to its rarity, these non-specific clinical findings of the disease cause a diagnostic challenge. During this pandemic, we recommend treating patients with a clinical suspicion to diagnose the rare manifestations of this disease. COVID-19-associated coagulopathy needs to be controlled even after COVID-related symptoms have resolved.

Table 1 Summary of the cases reported with renal infarction associated with COVID-19

Ref no	Age/gender	Presenting symptom	Uni/bilateral infarction	AKI	Treatment	Kidney outcome	Remarks	Survive
[5]	37/M	Flank pain	Bilateral	No	Lovenox, apixaban	CR	No comorbidities	Alive
[13]	39/F	Flank pain	Unilateral	No	Apixaban	CR	Obesity, HT, aortic thrombus	Alive
[14]	60 s/F	Respiratory symptoms	Bilateral	Yes	Apixaban, thrombectomy	CKD	AF, HT, bilateral complete occlusive thrombosis	Alive
[15]	62/M	Abdominal pain	Unilateral	NA	Heparin, oral anticoagulant	NA	HT	Alive
[16]	71/M	Respiratory symptoms	Unilateral	No	Heparin, clopidogrel, apixaban	CR	No comorbidities, ascending aortic thrombosis	Alive
[17]	64/M	Respiratory symptoms	Unilateral	NA	Enoxaparine, fondaparinux	CR	No comorbidities, aortic thrombosis, splenic infarct	Alive
[18]	62/M	Respiratory symptoms	Transplanted kidney	Yes	Dalteparin, acenocoumaroul	PR	HT, Henoch–Schönlein GN; living-related KTx	Alive
[18]	58/M	Respiratory symptoms + abdominal pain	Bilateral	Yes	Nadroparin	CR	Obstructive sleep apnea, bowel ischemia, CVVH, toe necrosis	Alive
[20]	41/F	Respiratory symptoms + abdominal pain	Bilateral	Yes	Enoxaparin	Died on HD	Obesity, diabetes mellitus, HD	Died
[21]	49/M	Respiratory symptoms	Transplanted kidney	Yes	Enoxaparin	Graft loss	Rejection and CMV colitis on history, biopsy-proven infarction	Alive
[22]	46/M	Abdominal pain	Transplanted kidney	Yes	Enoxaparin, apixaban	NA	Kidney-pancreas transplant history, readmission after hospital discharge	Alive
[23]	67/F	Flank pain	Unilateral	No	Fondaparinux	NA	Lobectomy for lung carcinoma, on chemotherapy, pneumonia after admission	Died

AKI, acute kidney injury; *M*, male; *F*, female; *CR*, complete remission; *PR*, partial remission; *HT*, hypertension; *CKD*, chronic kidney disease; *AF*, atrial fibrillation; *NA*, not available; *CVVH*, continuous venovenous hemofiltration; *HD*, hemodialysis

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