Pyelonephritis in an Immunocompromised Host Presented as a Drug Reaction-Like Syndrome

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Abstract

Introduction

Infection is the leading cause of death in patients on chronic immunosuppression. Diagnosis of infection in these patients can be challenging as immunosuppressants can blunt systemic inflammatory response and therefore elude ready detection.

Case presentation

We report an unusual case of pyelonephritis presenting as a drug reaction-like syndrome in a 49-year-old Caucasian male with crescentic IgA nephropathy on chronic immunosuppressants. His initial presentation was circulatory collapse without leukocytosis and leukocyturia. The episode occurred just days following the conversion cyclophosphamide to azathioprine, creating an impression that the rare azathioprine-associated anaphylactic reaction might have accounted for his symptoms. Azathioprine was held and he was empirically treated with antibiotics for three days, which led to symptom resolution. Few days later, he presented with another nearly identical episode, shortly after the re-initiation of azathioprine, further suggesting the possibility of drug reaction. His laboratory studies, however, were inconsistent with anaphylactic reaction. Eventually, the diagnosis of pyelonephritis was established by a kidney biopsy, showing intense interstitial polymorphonucleocyte infiltrates and numerous intratubular microabscesses. He recovered fully with an extended course of antibiotic treatment.

Conclusion

Immunosuppressive therapy can mask clinical manifestations of infection which, when unrecognized and untreated, can be life-threatening. This case illustrates the importance of maintaining a high vigilance and employing all available methods to investigate a potential source of infection in patients with impaired immunity.

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Introduction

Immunosuppression compromises the host defense and exposes patients to a variety of infections. In patients with glomerulonephritis on chronic immunosuppression, infection is the leading cause of death[1]. One of the most common bacterial infections is urinary tract infection (UTI) caused by pathogenic *Escherichia coli*[2]. Studies in recipients of organ transplantation show that when UTI occurs in patients on chronic immunosuppressants, it tends to be more severe and associated with a higher rate of complications, including septic shock and multiorgan failure[3], which could be rapidly fatal with a high (> 50%) mortality rate even under optimal management[4]. Additionally, immunosuppressants can blunt systemic inflammatory response; infections may not present with their typical symptomatology and therefore can elude ready detection. Under such circumstances, the search should be rigorous before the possibility of infection can be dismissed.

Case Presentation

A 49-year-old man with IgA nephropathy, hypertension, and type II diabetes was admitted to our hospital for fever, rigors, frontal headache, and lightheadedness of one-day duration. He was diagnosed 6.5 months prior with crescentic IgA nephropathy. His serum creatinine level was 177 µmol/L (53-97 µmol/L), and urine sediment active. After 6-month treatment with prednisone and cyclophosphamide, his serum creatinine stabilized at 106 µmol/L (GFR per MDRD 1.14 ml/sec/1.73m^2) and urine sediment became inactive. Cyclophosphamide was then replaced by azathioprine (75 mg twice daily) 16 days prior to the admission. He continued on prednisone 5 mg daily, lisinopril 20 mg daily, Losartan 50 mg daily, trimethoprim sulfamethoxazole DS (TMP/SMX) once every other day, and subcutaneous insulin injection. He had a complete urological work-up previously for hematuria which was unremarkable. The review of systems was

negative for version change, sore throat, cough, diarrhea, dysuria or urinary urgency.

Eleven days prior to the current admission (5 days after the switching from cyclophosphamide to azathioprine), he was admitted to a local hospital for the same symptoms of fever, rigors, headache and lightheadedness. His temperature was 39.5°C and BP 90/60 mmHg. He did not exhibit any focal abnormality. His WBC was 7.9 x 10^9/L. Urinalysis showed 4 WBC/HPF. Blood and urine cultures were negative. He was fluid resuscitated and received intravenous ceftriaxone and stress-dose steroids. Azathioprine was held. The shock-like symptoms resolved, but he was generally feeling unwell. He was discharged on the 3rd day without further antibiotics. Seven-days later, the prednisone dosage was tapered to the maintenance dose and he resumed azathioprine. Five hours after taking the medications, he started to experience nearly identical symptoms which led to the current admission.

On examination, he appeared ill. His temperature was 39.5°C, BP 93/42 mmHg, HR 116/min, and RR 28/min. His lung fields were clear, abdomen benign, flanks non-tender to percussion, skin no rash, extremities no edema, and neurologically non-focal. Laboratory studies were: HGB 10.5 g/dL, WBC 27.1x10^9/L (16 days off cyclophosphamide), Na 135 mmol/L (135-145 mmol/L), K 5.2 mmol/L (3.6-5.2 mmol/L), HCO3 19 mmol/L (22-29 mmol/L), Cl 103 mmol/L (100-108 mmol/L), Cr 220 µmol/L (53-97 µmol/L), BUN 16 mmol/L (2-7 mmol/L). Urine (via a urinary catheter, as he was oliguric on presentation, but reverted to being non-oliguric shortly after resuscitation) appeared concentrated but clear; microscopy showed RBC 4-10/HPF, WBC 31-40/HPF, and negative gram stain.

He was promptly volume resuscitated and empirically started on linezolid and cefepime. His immunosuppressants were replaced by stress-dose steroids. The provisional diagnosis was septic shock. However, given the recent similar episode which was temporally associated with the azathioprine initiation (negative infection work-up), and the symptoms of fever, headache, hypotension and leukocytosis which had been described in azathioprine-induced anaphylactic shock[5,6], azathioprine reaction was also suspected. Standard investigations for infection were undertaken. Blood and urine cultures, CT of head and abdomen, and lumbar puncture all failed to identify a source. To ascertain whether he had drug-induced anaphylactic shock, serum Tryptase and 24-hr urine N-Methylhistamine and 11β-Prostaglandin $F_{2\alpha}$ were obtained, as massive elaboration of these vasoactive mediators by circulating mast cells is the hallmark feature of anaphylactic reaction[7]. His serum Tryptase and urine N-Methylhistamine were within normal limits, 2.94 ng/mL (reference range: < 11.5 ng/mL) and 63 µg/gm creatinine (reference range: 30 - 200 µg/gm creatinine), respectively. His urine 11β-Prostaglandin $F_{2\alpha}$ was elevated, 2247 ng/24hr urine (reference range: ≤ 1000 ng/24 hr urine). This pattern was inconsistent with anaphylactic shock.

Despite lacking a clear source of infection, his symptoms improved with antibiotic treatment. By day 4, his fever defervesced, his WBC count reduced to 10.4 x 10^9/L, but his serum creatinine remained elevated at 220 µmol/L. Curiously, several repeat urine studies showed marked leukocyturia, > 100 WBC/HPF (persisted after urinary catheter removal) without eosinophiluria. Gram stains were negative, and he remained without urinary symptoms. Repeat abdominal CT and ultrasonography were unremarkable.

Given the persistent kidney dysfunction and puzzling urine microscopic findings, a diagnostic kidney biopsy was obtained at day 5 after admission. The biopsy showed tubulointerstitial disease with heavy interstitial neutrophilic infiltrates (**Figure 1A**), sloughing of tubular epithelial cells (**Figure 1B**) and numerous intratubular microabscesses (**Figure 1C**). The glomeruli showed mild mesangial expansion without endocapillary proliferation, necrosis or crescents. Immunofluorescent staining and electron microscopy confirmed background IgA nephropathy. These findings were consistent with acute pyelonephritis per imposed with tubular necrosis.

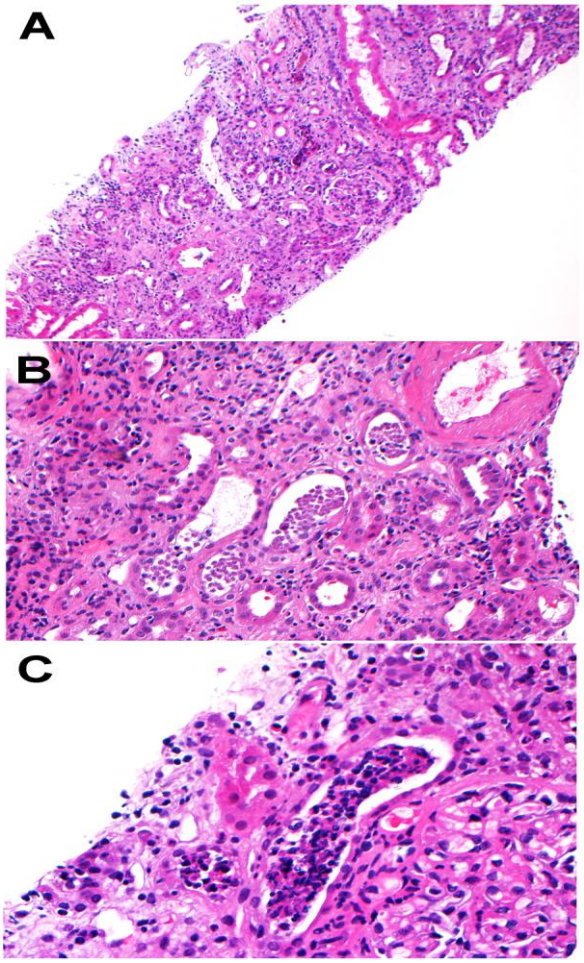

Figure 1. Hematoxylin and eosin staining of the kidney biopsy showing.
(A) Interstitial leukocyte infiltrates and tubular injury (10x).
(B) An area of acute tubular damage with denudation of tubular epithelium, sloughed tubular epithelial cells (arrows), and interstitial PMN infiltrates (20x).
(C) Tubular PMN casts/microabscesses (arrows) and interstitial PMN infiltrates (40x).

In light of the biopsy findings, he was given an extended (6-week) course of cefprozil. He responded with a complete resolution of leukocyturia, and a month later his serum creatinine level returned to 106 µmol/L. He continued regular follow-up at our Out-Patient Clinic.

Discussion

UTI/pyelonephritis is one of the most common infections in immunocompromised hosts and a major source of morbidity and mortality.[2,3] Pathogenic *Escherichia coli* is by far the most common pathogen, accounting for the vast majority of UTIs. In our patient, although blood and urine cultures were negative (possibly related to antibiotic exposure), his clinical and laboratory presentations, kidney biopsy findings, response to antibiotics, and the absence of other causes for his symptomatology (negative anaphylaxis workup) indicated that he had septic shock secondary to bacterial pyelonephritis.

UTI including pyelonephritis is the outcome of interaction between the bacteria virulence characteristics and the host defense mechanisms. Pathogenic *Escherichia coli* typically gain access to the gastrointestinal tract, and from there spread to the urinary tract and ascend to invade kidneys.

Pathogenic *Escherichia coli* adhere to the uroepithelium through their surface molecule adhesin (hair-like projections also termed p-fimbriae or pyelonephritis-associated pili). Adhesin also decreases IgA transport into the urine resulting in a reduction of local host defense.[8] Although polymorphonuclear cells (PMNs) do not possess adhesin receptor, they possess receptors binding to another group of pili of *Escherichia coli*, type I pili. The binding of PMNs and type I pili prevents bacteria adhesion to the uroepithelia. Although rare strains of *Escherichia coli* can shed their pili[9] thereby circumventing the effects of PMNs, in most circumstances, PMNs bind bacteria and protect hosts from infection. The pathogen in the current case was mostly likely *Escherichia coli*, as numerous epidemiologic studies indicating that they are the most common cause of UTI in immunocompromised hosts.[10]

With regard to the host defense, our patient had several deficiencies. First and perhaps most important, he had been under heavy immunosuppression for 6 months. Drug-induced marrow suppression prevented a robust leukemoid reaction to the infection. Second, secretory IgAs are known to participate in the maintenance of mucosal surface immune homeostasis and confer protection against pathogen colonization. Secretory IgAs also can neutralize bacteria PLS (important for *Escherichia coli* pathogenesis) independent of granulocyte cells or T-cells. Our patient had IgA nephropathy, which is pathogenetically related to defects in O-linked glycosylations. Such defects can alter the charge characteristics of IgA1 molecules. IgA1 with incomplete O-galactosylation also tends to self-aggregate,[9] thereby may diminish its physiological functions. Third, our patient has diabetes, which is one of the metabolic factors known to enhance bacterial invasiveness within urinary tract in immune compromised hosts.

Classically, history and physical examination are essential in identifying the existence and source of infection. In this patient, although he appeared in shock, a diagnosis of infection as an etiology of his presentation was called into question because (1) by history, he had been on TMP/SMX prophylaxis since the start of the immunosuppressive treatment and he did not show any focal (urinary) symptoms (might be related to the insufficient local leukemoid reaction, at least initially), and (2) on examination, he did not have flank pain or abdominal tenderness. This atypical presentation created a diagnostic dilemma.

Immunosuppressive therapy can mask the clinical manifestations of infection. Our patient did not have leukocytosis at his initial presentation to the local hospital, despite sepsis-like presentation. This is likely related to the marrow suppressive effect of cyclophosphamide. In line with this assumption, his serum leukocyte counts (and urine leukocytes) were increased in the succeeding days as more time elapsed from the last dosage of cyclophosphamide, consistent with a gradual recovery of leukemoid response to infection. Although the steroid administration during his hospital stay could have contributed to the leukocytosis, it was unlikely to have been a major factor because the leukocytosis on admission preceded the initiation of stress-dose steroids. Thus, the initial lack of leucocytosis was likely related to drug-associated marrow suppression. Incidentally, this case also served to dispel the notion that patients on TMP/SMX prophylaxis would not be at risk for UTI. Our patient developed pyelonephritis while on TMP/SMX, and recent studies also show that over 70% uropathogenic bacteria are insensitive or resistant to TMP/SMX[11].

Although infection, given its potential fatality, should be doggedly pursued, it is plausible to include multiple diagnostic considerations. The atypical presentations in this case led to seeking alternative explanations, such as pseudo-sepsis due to drug reaction.

Azathioprine is an imidazole derivative of 6-mercaptopurine. The allergic-type reactions have been described as a rare and dose-independent event occurring within days to weeks following the drug introduction.[6] The reactions can range from pancreatitis, hepatitis, skin rash, fever, arthralgias, malaise, diarrhea and abdominal pain to anaphylactic shock. The anaphylactic reaction/shock is characterized by abrupt onset of headache, fever, hypotension and leukocytosis.[5,6] Although our patient's presentation fit well with this description, his laboratory studies did not. In a typical anaphylactic reaction, circulating mast cells are acutely activated, releasing a host of vasoactive mediators including tryptase, histamine, and prostaglandin D2. Serum and urine levels of these mediators and their metabolites, N-Methylhistamine and 11β-Prostaglandin $F_{2\alpha}$, are expected to be massively and simultaneously elevated. Our patient had an isolated elevation of 11β-Prostaglandin $F_{2\alpha}$, inconsistent with anaphylactic reaction.[7] In fact, the isolated 11β-Prostaglandin $F_{2\alpha}$ elevation (to the level comparable to that in our patient) can be seen in physiologic conditions during normal labor[12] or sleep[13]. Under these circumstances 11β-Prostaglandin $F_{2\alpha}$

is released from tissues rather than from circulating mast cells. Thus, the isolated 11β-Prostaglandin $F_{2\alpha}$ elevation in this case can not be attributed to anaphylactic reaction.

Recently, rare cases of acute allergic interstitial nephritis have been described in patients taking azathioprine[14,15]. Such reaction is associated with skin rash and transient hypocomplementemia, and kidney biopsy shows monocytic/lymphocytic infiltration mixed with prominent eosinophiles. Our patient had neither rash nor hypocomplementemia; his kidney biopsy showed PMN predominance and numerous microabscesses, inconsistent with an allergic type reaction. The kidney biopsy in our case helped to resolve the diagnostic dilemma and to design a therapeutic plan.

Conclusion

Diagnosing infection in patients with immunosuppression can be exceedingly challenging. Medications such as azathioprine can cause a clinical picture mimicking septic shock. When infection is suspected and standard evaluation fails to identify a source, additional investigations (i.e., kidney biopsy in this case) not routinely conducted in non-immunocompromised hosts may be indicated to facilitate diagnosis and management.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

QQ was involved in patient care and manuscript writing. MHS contributed to the literature review and the manuscript writing, and SS to the kidney histological examination and manuscript writing. All authors read and approved the final manuscript.

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