Non-Surgical Treatment of Retroperitoneal Hemorrhage and Urinary Bladder Perforation

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Retroperitoneal hemorrhage is an uncommon complication of femoral artery catheterization but can occur spontaneously. We present a novel association between cryoglobulinemia and retroperitoneal hemorrhage. In this case communication we describe a urinary bladder perforation due to a rupture of an infected retroperitoneal hematoma that was treated successfully with conservative measures.

PATIENT DESCRIPTION

A 50 year old female was transferred to our medical center from another hospital due to life-threatening shock and rapid deterioration in renal function. Past medical history included chronic lymphoid leukemia, which was stable at RAI stage 0, cryoglobulinemia since 2001 and hypertension. Of note, in a previous flare of cryoglobulinemia she had presented with renal impairment, later diagnosed as membranoproliferative glomerulonephritis. She was treated successfully with methylprednisolone and cyclophosphamide and regained normal renal function.

Her current illness started in late August 2009 as she presented with acute symptomatic anemia after a trip abroad. She reported rectal bleeding 8 days prior to her admission, which she had dismissed as she had a known history of hemorrhoids. On arrival at the medical facility, the patient was pale and alert, yet weak. Physical examination revealed a soft but tender abdomen without signs of peritoneal irritation or signs of active external bleeding. Blood count revealed a hemoglobin level of 4.5 g/dl (normal range is 12–16 g/dl) with a normal platelet count. Coagulation studies were unremarkable as was kidney function, with a normal creatinine level of 0.8 mg/dl. Four units of blood were administered and hemoglobin rose to 10 g/dl. Colonoscopy demonstrated large prolapsed hemorrhoids and a 7 mm polyp on a stalk in the splenic flexure, which was resected. The patient was discharged in good clinical status with a diagnosis of presumed gastrointestinal bleeding.

Five days after her initial presentation the patient was readmitted with fatigue, significant weight gain, peripheral edema and oliguria. Acute renal failure was found with a creatinine level of 2.3 mg/dl. There was no significant proteinuria and the urine sediment was bland. Findings did include marked hypocomplementemia with C3 of 66 (normal range is 90–180) and C4 of 1.99 (normal range is 10–40) and a cryocrit of 5%. Hemoglobin was stable compared to the previous admission.

Due to progressive kidney failure, 5 days after admission a temporary dialysis catheter was inserted into the right femoral vein. Following the procedure severe right inguinal pain developed. Computed tomography (CT) angiography of the abdomen and pelvis demonstrated retroperitoneal hemorrhage [Figure 1A]. Hemoglobin level dropped to 5.7 g/dl. Angiography was performed and a small branch of the right external iliac artery was embolized. The following day a second procedure was required to treat bleeding from a branch of the right internal iliac artery. The right

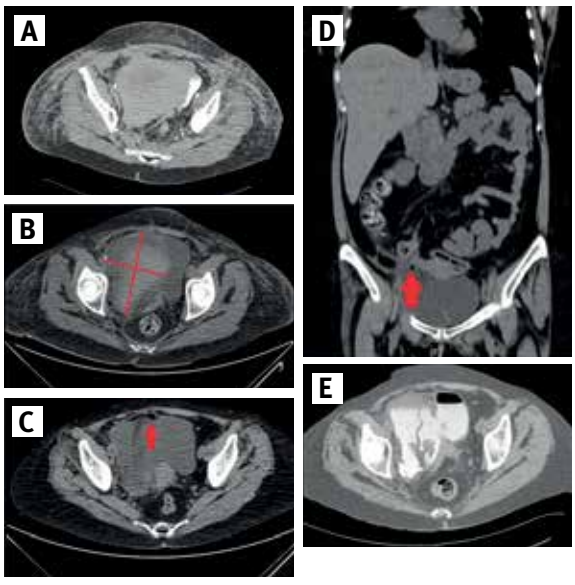

Figure 1. A-E consecutive CT imaging.

[A] Large hematoma compressing the bladder (day of presentation)

[B] Hematoma 1 month after presentation, reaching a size of 12.3 cm × 87.8 cm

[C] and **[D]** Third admission (2 months after presentation): air bubble (red arrow) not observed before.

[E] Extravasation of contrast material injected through a urinary catheter

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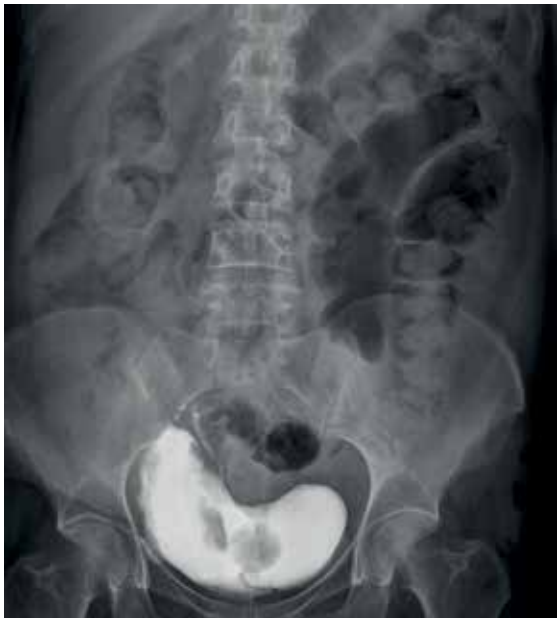
Figure 2. Cystogram



femoral dialysis catheter was replaced with a jugular catheter.

At this point the patient was transferred to our facility and required inotropes and dialysis. Kidney biopsy revealed glomerulonephritis consistent with cryoglobulinemia, and thus she was treated with steroids, a single pulse of cyclophosphamide (after fluids and MESNA preparation) and 12 cycles of plasmapheresis with complete resolution of renal failure.

Immediately after cyclophosphamide administration she suffered from gross hematuria which resolved spontaneously. During her 1 month hospital stay she developed multiple infections, including several urinary tract infections with bloodstream infections and sepsis for which she received several antibiotic regimens.

Upon discharge the patient was hemodynamically stable, afebrile and clinically improving. A repeat CT angiography performed 1 month after the initial bleeding showed a large hematoma pressing on the urinary bladder, although it had decreased in size [Figure 1B]. It was decided to refrain from drainage and the patient was discharged for outpatient follow-up with a steroid taper and low dose azathioprine. The following 2 months were marred by two hospital admissions due to urosepsis, which was treated with antibiotics according to culture results. Interestingly, in the three described admissions, urine cultures were positive for different bacteria (*Psedomonas aeruginosa, Enterobacter cloacae,* and *Klebsiella pneumoniae*).

During her third admission with urosepsis, a CT examination revealed new air bubbles in the hematoma, suggesting a transformation to infected hematoma/abscess [Figures 1C and 1D]. Further evaluation by CT with contrast media inserted through a urinary catheter and a cystogram demonstrated a perforated urinary bladder with contrast media extravasation [Figure 1E and Figure 2]. Surgery to drain the abscess and repair the bladder was considered but deemed risky due to the notable fragility of the bladder wall. However, an attempt at conservative treatment was judged to be reasonable as the patient was no longer receiving immunosuppression and, more importantly, the abscess achieved natural effective drainage via its communication with the bladder lumen. The patient therefore received long-term broad spectrum antibiotic treatment (ertapenem intravenously) along with an indwelling urinary catheter. Antibiotic treatment was stopped after 2 months. The urinary catheter was removed after an additional month following cystography which showed an un-bridged urinary bladder.

Six years after these dramatic events the patient is doing remarkably well with no sequelae and no clinical or serologic activity of her rheumatologic disease.

COMMENT

We present a unique case of an infected retroperitoneal hematoma which spontaneously canalized through the urinary bladder toward complete clinical and anatomical resolution. Retroperitoneal hemorrhage is a rare phenomenon whose major causes include trauma, bleeding from a retroperitoneal organ (e.g., adrenal gland), aneurysm and femoral artery catheterization. Femoral vein catheterization was described as a cause, either due to venous bleeding or to inadvertent arterial puncture [1].

Like other vasculitides, cryoglobulinemia is known to be associated with bleeding diathesis such as alveolar hemorrhage [2,3]. Other vasculitides, particularly polyarteritis nodosa, are known causes of retroperitoneal hemorrhage, all purportedly due to increased vascular fragility. However, to the best of our knowledge, cryoglobulinemia has not been previously associated with retroperitoneal hemorrhage. The rapid development of symptoms and the hemoglobin decrease hours after the femoral venous catheterization strongly suggest a causal relationship. However, the significant asynchronous bleeding from two distinct arterial sites implies that bleeding resulted from the combination of vascular manipulation and a substrate of diseased vessels.

Spontaneous rupture of the urinary bladder is rare, although occasionally reported. Several case reports and series suggest different etiologies, which include weakening of the bladder wall, increased intravesical pressure (such as with a bladder outlet obstruction) and bladder disease (e.g., cystitis, neoplasm) [4].

Cyclophosphamide is known for its ability to cause bladder disease or hemorrhagic cystitis, which could presumably have led to a bladder perforation in our patient. However, this condition is unlikely as such incidents have not been described and cystitis typically develops 1 to 2 days after treatment. Whereas in our patient perforation developed months later.

A retroperitoneal hematoma as a cause of bladder perforation has been described only once, to the best of our knowledge, in a case report by Lane et al. [5]. They described a 71 year old patient who developed retroperitoneal bleeding from a femoral artery injured during coronary catheterization. The patient presented 2 days later with gross hematuria and a tender abdomen. Imaging studies demonstrated a ruptured bladder. The rupture was attributed to pressure necrosis formed by the hematoma and an indwelling catheter. Conservative management was first attempted but after 12 weeks without closure of the perforation,

the patient underwent exploratory surgery and repair. Of note, our patient did not have an indwelling urinary catheter at the time of the perforation.

In our case, it is unknown whether infection of the hematoma preceded the fistulization to the bladder or whether bacterial invasion of the hematoma occurred only following communication with the infected bladder. It seems most plausible that a combination of pressure necrosis with local infection and inflammation led to the bladder perforation. As the vasculitis was in remission and cyclophosphamide exposure remote, their contribution was presumably partial at best.

CONCLUSIONS

We present a case suggesting a contribution of cryoglobulinemia to iatrogenic femoral artery bleeding leading to the formation of a retroperitoneal hematoma, which was subsequently infected. A basic paradigm in medicine states that abscesses need to be drained and thus retroperitoneal abscesses are routinely treated surgically or percutaneously. Our case is unique in demonstrating that as effective drainage was achieved spontaneously, a trial of conservative treatment under observation can be a reasonable option, possibly obviating the need for invasive modalities.

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Capsule

Nanoparticles for drug delivery in lungs

Engineering drug-delivery nanoparticles for adhesion to mucus can increase their residence times in lungs. Schneider and colleagues alternatively developed mucus-penetrating nanoparticles that exhibited greater retention in the lung and enhanced drug-delivery capability. Retention was related to the size of the particles; those smaller than the average mesh spacing of airway mucus were able to penetrate it, thus defeating physiologic mucus clearance. The result was a more effective and uniform distribution of the particles within the mucus and greater efficacy in a mouse model of acute lung inflammation.

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Eitan Israeli

Capsule

Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis

Adaptive thermogenesis is the process of heat generation in response to cold stimulation. It is under the control of the sympathetic nervous system, whose chief effector is the catecholamine norepinephrine. Norepinephrine enhances thermogenesis through β3-adrenergic receptors to activate brown adipose tissue and by 'browning' white adipose tissue. Recent studies have reported that alternative activation of macrophages in response to interleukin (IL)-4 stimulation induces the expression of tyrosine hydroxylase (TH), a key enzyme in the catecholamine synthesis pathway, and that this activation provides an alternative source of locally produced catecholamines during the thermogenic process. Fischer and colleagues reported that the deletion of TH in hematopoietic cells of adult mice neither alters energy expenditure upon cold exposure nor reduces browning in inguinal adipose tissue. Bone marrow-derived macrophages did not release norepinephrine in response to stimulation with IL-4, and conditioned media from IL-4-stimulated macrophages failed to induce expression of thermogenic genes, such as uncoupling protein 1 (*Ucp1*), in adipocytes cultured with the conditioned media. Furthermore, chronic treatment with IL-4 failed to increase energy expenditure in wild-type, *Ucp1*$^{-/-}$, and interleukin-4 receptor-α double-negative (*Il4ra*$^{-/-}$) mice. In agreement with these findings, adipose-tissue-resident macrophages did not express TH. Thus, the authors concluded that alternatively activated macrophages do not synthesize relevant amounts of catecholamines, and hence, are not likely to have a direct role in adipocyte metabolism or adaptive thermogenesis.

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"When I hear somebody sigh, 'Life is hard,' I am always tempted to ask, 'Compared to what?'"

Sydney J. Harris (1919-1986), American journalist for the *Chicago Daily News* and, later, the *Chicago Sun-Times*