CASE REPORT

Graft-versus-host disease: unexpected presentation with simultaneous hepatitis and pancreatitis

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SUMMARY

We report the case of a 37-year-old man with a previous bone marrow transplantation presenting with abdominal pain, diarrhoea and jaundice. Laboratory evaluation showed marked elevated liver enzymes, amylase and lipase with ultrasonographic evidence of acute althiasic pancreatitis. Liver biopsy was compatible with graft-versus-host disease and toxic hepatitis. The patient rapidly improved after increasing immunosuppression. Although gastrointestinal manifestations are common in graft-versus-host disease, clinical acute pancreatitis is rarely seen. Patients with graft versus host are seldom managed by gastroenterologists and hepatologists. An awareness of this condition is essential for the experienced clinician.

BACKGROUND

The number of allogeneic haemopoietic-cell transplantations (AHCT) continues to rise with >21 000 procedures performed every year worldwide.¹ Graft-versus-host disease (GVHD) remains the major complication of AHCT. Acute and chronic forms have traditionally been defined based on the timeframe post-transplant (less than or greater than 100 days, respectively), but current consensus is that clinical manifestations guide whether the signs and symptoms of graft-versus-host disease are acute, chronic or an overlap syndrome. Acute GVHD can result in damage to the liver, skin, gastrointestinal tract and unusually the bone marrow, thymus and lungs. Chronic GVHD can affect the aforementioned organs and, in addition, damage the joints, connective tissue, neuromuscular system and exocrine glands.² This case is peculiar due to the uncommon presentation and differential diagnosis. We appraise the clinical and anatomopathological findings, discuss treatment and prognosis, and review the available literature.

CASE PRESENTATION

A 37-year-old black African man was admitted to our department with abdominal pain, diarrhoea, vomiting and jaundice. His medical history was significant for acute lymphoblastic leukaemia diagnosed 1 year before. Following ablative chemotherapy, he received a bone marrow allograft from a related donor. He had since been hospitalised multiple times due to infectious complications, and required several antimicrobial regimens, including antibiotics, antivirals and antifungals.

Three months earlier, during a hospitalisation for a urinary tract infection, the patient presented with

a severe bout of epigastric pain radiating to the back. His laboratory tests revealed an elevated amylase (1640 U/L, normal range <53) and lipase (2425 U/L, normal range <60), and the abdominal CT showed a diffuse enlargement and globosity of the pancreas with peripancreatic exudates extending to the pararenal fascia and the psoas-iliac muscles compatible with an acute complicated pancreatitis. The patient improved following supportive therapy. The aetiology of the acute pancreatitis remained obscure after exclusion of bile duct stones and infection with HIV, hepatitis A, B, C, Herpes simplex, cytomegalovirus (CMV) and Epstein-Barr virus. There was no personal history of alcohol, tobacco, drug use or recent travelling. There was no family history of liver or pancreatic disease. By the time of his current admission, the patient was receiving immunosuppression with mycophenolate mophetil (500 mg two times per day), prednisolone (5 mg once daily) and ciclosporin (25 mg once daily). Five days before admission, the patient had epigastric discomfort and watery diarrhoea (3–4 bowel movements/day). Twelve hours before admission, the pain became severe and spread to the upper abdomen and back. He also developed low-grade fever, nausea and vomiting. At admission, the patient had jaundice and showed severe upper abdominal tenderness on palpation, with no other remarkable findings. Laboratory tests showed elevation in aminotransferases, γ -glutamyl transpeptidase, total bilirubin, serum amylase and lipase. Table 1 shows the patient's laboratory evaluation during the previous admission, 1 month before and at the current admission.

Abdominal ultrasound showed an enlarged hypoechoic pancreatic head compatible with acute pancreatitis. There was no evidence of cholecystitis, bile duct dilation or gallstones. The patient was admitted for further investigation.

INVESTIGATIONS

HIV, hepatitis A, B, C, Herpes simplex, adenovirus, CMV and Epstein-Barr virus were negative. CMV viral load was undetectable. Serologies for leptospirosis, *Mycoplasma pneumoniae* and syphilis were negative. Blood cultures showed no growth for bacteria, mycobacteria and fungus. Antidouble-stranded DNA, antinuclear, anticytoplasmic, anti-Liver Kidney Microsome (anti-LKM), antimitochondrial, anti-smooth muscle and celiac antibodies were negative. CA 19.9 (33.4 U/mL, normal range <37), thyroid-stimulating hormone (3.99 μ U/mL, normal range 0.55–4.78), parathyroid hormone (22.3 pg/mL,

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Table 1 Laboratory evaluation of our patient

Item	Previous admission	1 month before the current admission	At admission	Normal values
ALT (U/L)	48	57	138	12–78
GGT (U/L)	204	317	522	<38
Total bilirubin (mg/dL)	0.48	0.62	5.1	<1.0
Amylase (mg/dL)	1640	50	392	13–53
Total lipase (mg/dL)	2425	–	1037	13–60

ALT, alanine aminotransferase; GGT, γ -glutamyl transpeptidase.

normal range 14–72), serum calcium (9.3 mg/dL, normal range 8.6–10.2), triglycerides (174 mg/dL, normal range <150) and total γ -globulin (IgG) (1.1 g/dL, normal range 0.71–1.41) and IgG4 (11 mg/dL, normal range 4–86) were within normal values. Stool examination showed several leucocytes, but the microscopic examination was negative. The CT showed no significant pancreatic abnormalities, including (peri)pancreatic necrosis or exudates but revealed a significant thickening of the caecum and ascending colon wall. Colonoscopy with histopathology of random biopsies was normal. As the liver alterations remained unexplained, a liver biopsy (figures 1 and 2) was performed showing moderate macrovacuolar and microvacuolar steatosis; parenchymal and perisinusoidal fibrosis; focal ductopenia and irregularity in bile duct epithelium with eosinophilia and vacuolisation; moderate mixed inflammatory infiltrate (lymphocytes, plasmocytes, eosinophils and neutrophils) with focal endotheliitis, hepatocellular necrosis; cholestasis and ballooning. These findings, although compatible with GVHD, could not exclude a superimposed toxic event.

DIFFERENTIAL DIAGNOSIS

Our patient had no evidence of gallstones, the major cause of acute pancreatitis. All viral and bacterial serologies performed were negative making this aetiology unlikely. The biochemical investigation, including serum calcium, thyroid and parathyroid hormones, was also normal. Our investigation for autoimmune conditions (which included IgG4) was also negative making this hypothesis unlikely. Our patient had taken several drugs, all known to potentially cause drug-induced hepatitis. A review of the literature suggests that either ciclosporin or meropenem would fit as the most probable culprits. On the other hand, this clinical scenario coincided with a lowering of his immunosuppressive medication, suggesting that an immune-mediated event like GVHD could be the cause. The patient's gastrointestinal

Figure 1 Pathological findings (H&E, A— $\times 40$, B— $\times 400$). Moderate microvesicular and macrovesicular steatosis of irregular distribution with mixed inflammatory infiltrate surrounding the portal tract (A). Bile duct lesion with eosinophilia and cytoplasm vacuolation and endotheliitis with hyperchromatic nuclei (B).

Figure 2 Pathological findings (H&E, A and B, $\times 400$, Masson's trichrome stain, C, $\times 400$). Hepatocellular damage evidenced by focal necrosis (black arrow) and hepatocyte ballooning (white arrow) (A), acidophilic bodies (B) and perisinusoidal fibrosis (C).

symptoms could also favour GVHD. Therefore, the differential diagnosis should include drug-induced hepatitis and GVHD.

TREATMENT

After excluding infection, we adjusted the patient's immunosuppressive regimen by increasing prednisolone to 2 mg/kg/day and mycophenolate mophetil to 1 g two times per day.

OUTCOME AND FOLLOW-UP

This action resulted in a marked improvement of all liver tests (figure 3). The patient was discharged after 10 days of admission. Follow-up of 1 month later showed a sustained improvement in the patient's condition. On the following year, he presented no additional episodes of pancreatitis or hepatitis.

DISCUSSION

About half of all AHCT will develop GVHD. The exact risk is dependent on the stem cell source, age of the patient, conditioning and GVHD prophylaxis used. Liver disease caused by GVHD can be difficult to distinguish from other causes of liver dysfunction such as drug-induced hepatitis, viral infection, sepsis and gallstone disease. Liver biopsy is rarely performed in this setting but can show typical findings like endotheliitis, portal lymphocytic infiltration, pericholangitis and ductopenia.

Figure 3 Laboratory panel showing a decrease in liver tests following intensification of the immunosuppressive regimen.

Severe GVHD has a poor prognosis, with a 5-year survival between 5% and 25%.³ The diagnosis of acute pancreatitis rests on a combination of typical symptoms (upper abdominal pain radiating to the back), elevated serum amylase and lipase (more than three times the upper normal range) and compatible imaging studies. Our patient filled all three criteria. Despite having no evidence of acute pancreatitis on CT, his ultrasound at admission showed mild pancreatic alterations. It is a known fact that in mild pancreatitis, CT may present a normal-appearing pancreas with no pancreatic abnormalities.⁴ Furthermore, on his previous admission, our patient presented with an acute pancreatitis with local complications (peripancreatic exudates or necrosis) further supporting the diagnosis. Although chronic pancreatitis is a recognised complication of chronic GVHD,⁵ acute pancreatic disease is seldom considered in the setting of GVHD. However, this may result from under-recognition of this complication. In 57 patients submitted to haematopoietic stem cell transplantation, Kawakami *et al*⁶ reported an elevated amylase in 21% and overt acute pancreatitis in three patients. The author also established a correlation between severity of GVHD and pancreatic amylase. In an older study by Salomone *et al* investigating 26 patients undergoing AHCT, a diagnosis of acute pancreatitis using amylase, lipase, abdominal ultrasound and contrast-enhanced tomography was performed in three patients. The autopsy report of one of the patients who died from multiple organ failure showed evidence of interstitial acute pancreatitis.⁷ Unfortunately, underlying GVHD may be a confounder, as most AHCT are carried out on an immunosuppression regimen with drugs known to cause organ toxicity.

Some authors have suggested that the distinction of these two entities may be made using histopathological features (centrilobular hepatocyte oedema, fatty change and intrahepatic cholestasis) or drug lymphocyte-stimulating tests.⁸ However, as in our case, a clear histological distinction between these two entities is not always possible. Furthermore, lymphocyte-stimulating tests are not routinely available in most centres. A comment should be made regarding our patient's gastrointestinal findings. Our patient presented with loose non-bloody diarrhoea which could be interpreted as a manifestation of the GVHD. The stool examination showed increased leucocytes with no evidence of underlying infection (negative microscopic examination and culture with negative *Clostridium difficile* test) and the abdominal CT showed bowel wall thickening. These findings could be consistent with an inflammatory condition such as GVHD. Nevertheless, we can only speculate over this association as the patient's endoscopy did not show any macroscopic findings.

Although the histopathological examination was normal, we emphasise that these were random biopsies of normal mucosa making it possible that focal low-grade inflammation might have been missed.

In conclusion, GVHD represents a challenging complication of AHCT, commonly affecting the gastrointestinal system. Although most haematological patients are admitted directly to specialist units, an awareness of these conditions is essential for the experienced gastroenterologist and hepatologist.

Learning points

- ▶ GVHD is a common under-recognised cause of abnormal liver tests and gastrointestinal symptoms after stem cell transplantation.
- ▶ Treatment of GVHD involved immunosuppression. Every attempt should be made at differentiating GVHD from other causes of liver dysfunction, including drug-induced liver injury, viral hepatitis, sepsis and gallstone disease.
- ▶ Liver biopsy may be helpful in the differential diagnosis.

Contributors SRF, MBC and ATA elaborated the manuscript; HC-P reviewed the manuscript and provided important insight.

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REFERENCES

- 1 Gratwohl A, Baldomero H, Aljurf M, *et al*. Hematopoietic stem cell transplantation: a global perspective. *JAMA* 2010;303:1617–24.
- 2 Ratanatharathorn V, Ayash L, Lazarus HM, *et al*. Chronic graft-versus-host disease: clinical manifestation and therapy. *Bone Marrow Transplant* 2001;28:121–9.
- 3 Garnett C, Apperley JF, Pavlů J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol* 2013;4:366–78.
- 4 Koo BC, Chinogureyi A, Shaw AS. Imaging acute pancreatitis. *Br J Radiol* 2010;83:104–12.
- 5 Akpek G, Valladares JL, Lee L, *et al*. Pancreatic insufficiency in patients with chronic graft-versus-host disease. *Bone Marrow Transplant* 2001;27:163–6.
- 6 Kawakami T, Mitsui T, Sando D, *et al*. Acute pancreatitis following hematopoietic stem cell transplantation: prevalence and cause of pancreatic amylaseemia. *Rinsho Ketsueki* 2002;43:176–82.
- 7 Salomone T, Tosi P, Raiti C, *et al*. Clinical relevance of acute pancreatitis in allogeneic hemopoietic stem cell (bone marrow or peripheral blood) transplants. *Dig Dis Sci* 1999;44:1124–7.
- 8 Takikawa H. Recent status of drug-induced liver injury. *Hepatol Res* 2009;39:1–6.

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