The abdominal manifestations of the antiphospholipid syndrome

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Objective. To study the abdominal manifestations of the antiphospholipid syndrome (APS).

Methods. We reviewed the medical literature from 1968 to 2006 using MEDLINE and the key words: APS, antiphospholipid antibodies, lupus anticoagulant, antiphospholipid (aPL) antibodies, catastrophic antiphospholipid syndrome, liver, hepatic biliary, pancreas, spleen, gastrointestinal and abdominal.

Results. Liver involvement is the most frequent abdominal manifestation associated with APS. Various hepatic manifestations have been reported, including Budd-Chiari syndrome, hepatic-veno-occlusive disease and occlusion of small hepatic veins, nodular regenerative hyperplasia, hepatic infarction, cirrhosis, portal hypertension, autoimmune hepatitis and biliary cirrhosis. Acute intestinal infarction, intestinal obstruction of the outflow of hepatic venous blood [3]. BCS is clinically characterized by abdominal pain, hepatomegaly and ascites, and the clinical presentation may range from almost asymptomatic to fulminant liver failure [4].

Hepatic manifestations

A wide range of hepatic diseases have been reported in association with the presence of aPL, these vary from thrombosis of major arterial or venous beds to microthrombotic conditions. Moreover, non-thrombotic liver diseases have also been reported in the context of APS.

Introduction

Antiphospholipid syndrome (APS) is characterized by a state of hypercoagulability potentially resulting in thrombosis of all segments of the vascular bed [1]. Since the initial description of this syndrome, thrombotic manifestations involving the liver have been reported [2]. Thereafter, a wide range of hepatic manifestations, in addition to thrombotic events involving various other intra abdominal organs were published. Some of these conditions may be life threatening, necessitating a high index of suspicion for their early recognition. The objective of this article is to define and classify the abdominal manifestations of the APS by reviewing published reviews and case reports on this topic.

Materials and methods

We undertook a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature up until 2006, using the keywords: APS, antiphospholipid antibodies (aCL), lupus anticoagulant (LA), antiphospholipid antibodies (aPL), catastrophic APS (CAPS), liver, hepatic biliary, pancreas, spleen, gastrointestinal (GI), and abdominal. The relevant papers were grouped according to the involved organs and further subclassified by different disease entities in each group.

Results

Hepatic involvement was the most common of the APS abdominal manifestations, followed by thrombotic events involving different branches of the intestinal vasculature. Sporadic cases of splenic infarction and acute pancreatitis were reported. Table 1 summarizes the major abdominal manifestations associated with APS, classified according to the involved organs.
TABLE 1. Summary of the abdominal manifestations associated with the antiphospholipid syndrome

<table>
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<th>Abdominal Organ</th>
<th>Manifestations</th>
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| Liver           | Budd-Chiari Syndrome:  
|                 | Hepatic-veno-occlusive disease and occlusion of small hepatic veins  
|                 | Nodular regenerative hyperplasia  
|                 | Cirrhosis  
|                 | Portal hypertension  
|                 | Autoimmune hepatitis  
|                  | Biliary cirrhosis  
|                  | Liver transplantation  
| Intestine       | Acute intestinal infarction  
|                  | Intestinal angina  
|                  | Intestinal bleeding  
|                  | High prevalence of aPL but no increased vascular thromboses in inflammatory bowel disease  
| Spleen          | Splenic infarction  
|                  | Autosplenectomy or functional asplenia  
| Pancreas         | Acute pancreatitis |

The pathogenic role of aPL in BCS is controversial. Some authors suggest that the liver abnormalities caused by the venous outflow obstruction could be involved in the production of these antibodies, which would then be just an epiphenomenon secondary to the liver damage [20]. However, in some cases aPL were detected before the onset of BCS strongly suggesting that the production of aPL was not a consequence of the liver abnormalities [4].

In conclusion, BCS may be the first clinical manifestation of APS. Therefore, this syndrome should be considered in the differential diagnosis of hepatic vein thrombosis, and measurement of the LA and aCL levels should be routinely carried out in these patients [4].

**Hepatic-veno-occlusive disease and occlusion of small hepatic veins**

Hepatic-veno-occlusive disease (HVOD), an unusual hepatic disorder characterized by hepatomegaly and ascites, is a common complication of bone marrow transplantation. The association between HVOD and APS was first suggested by Pappas et al. [21] in a patient with systemic lupus erythematosus (SLE) who developed the condition. Since then only very few cases with aPL in association with HVOD have been documented [22, 23].

Oclusion of small hepatic veins differs from HVOD by the absence of endophlebitis on liver biopsy. Several cases of histologically proven occlusion of small hepatic veins were reported [24–28].

**Hepatic infarction**

Although hepatic infarction is a rare entity, due to the dual blood supply to the liver, several cases of hepatic infarction have been reported in association with APS [29–36]. In 1989 Mor et al. [29] reported the first case of hepatic infarction in a pregnant patient with positive LA. Kinoshita reported a case with recurrent hepatic infarction in her first and third pregnancies [31]. Millan-Mon et al. [33] described a case of massive hepatic infarction in the third trimester of pregnancy in a patient with PAPS. In a retrospective review of the abdominal computer tomographic scans of 215 APS patients, out of 42 patients with abdominal thrombosis only one patient with hepatic infarction was reported [36]. APS should be considered as a possible cause of hepatic infarction, and measurement of aPL is warranted in this condition especially in pregnancy.

**Liver transplantation**

Hepatic artery thrombosis (HAT) is a main cause of graft loss and patient mortality after liver transplantation. Since many of the hepatic conditions leading to liver transplantation are associated with elevated levels of aPL, the role of these antibodies post-transplant thrombosis has been carefully investigated, with conflicting results.

Vivarelli et al. [37] in a study on 24 patients who underwent retransplantation for HAT, out of 624 consecutive liver transplants, detected aPL in 3 of these patients. The authors advised careful screening for aPL in the pre-transplant workup. On the other hand, in another study by Van Thiel et al. [38] to determine whether liver transplantation of patients with aPL is adversely affected with vascular thrombosis and whether such antibodies persist post transplantation, they identified 12 pre-transplant patients with aPL and followed them up post transplant. On follow-up no patient experienced a transplant-related vascular thrombosis, and the titre of aPL fell to levels at or below those present in normals and remained low in 2 of 12 or undetectable in 10 of 12 patients 1 yr after liver transplantation. The authors concluded that aPL positivity does not identify patients at high risk for post-transplant vascular thrombosis, and the levels of aPL in pretransplant sera fell during transplantation and remained low or undetectable 1 month and 1 yr post-transplantation [38].

Despite these conflicting reports careful screening for aPL in liver pre-transplant patients and close follow-up for signs of HAT in aPL positive patients may be warranted.

**Non-thrombotic liver diseases**

**Nodular regenerative hyperplasia (NRH).** Nodular regenerative hyperplasia (NRH) of the liver or non-cirrhotic portal hypertension, is an uncommon disorder which is characterized by the transformation of the liver parenchyma into nodules of hyperplastic hepatocytes without fibrosis [39]. Several reports have documented a relationship between NRH & APS. [32, 40–44]. Perez-Ruiz et al. first suggested a role for aPL in the pathogenesis of NRH, four out of seven patients with rheumatic disorders and NRH, had positive LA test [40, 41]. Keegan et al. [32] later reported the case of a young female with acute congestive hepatic infarction and aCL antibodies who subsequently developed NRH and suggested that NRH may develop as a consequence of diminished hepatic venous drainage. Sera from 13 patients with histologically defined NRH were tested for aPL, 77% of the NRH patients had aPL compared with 14% of the patients with autoimmune liver diseases and healthy controls (P < 0.05) [44].

Although a causal relationship between aPL and NRH is not clearly established, suggesting that they may be an immunological epiphenomenon, determination of these antibodies may still be warranted.

**Cirrhosis.** The presence of aPL in patients with liver cirrhosis has been reported in few cases, with conflicting reports on the pathogenicity of the thrombotic potential of these antibodies. In 1994 Talenti et al. [45] reported the first case of a thrombotic vascular occlusion in association with elevated levels of aCL in a patient with a 30-yr history of cryptogenic cirrhosis. A close association between the severity of alcoholic liver cirrhosis and the presence of aPL was reported by Chedid et al. [46]. Gervais et al. [47] in a study on patients with alcoholic liver cirrhosis complicated by hepatocellular carcinoma reported a significantly higher frequency of aPL in these patients however no association with the presence of thrombosis could be identified. Recently Perney et al. [48] showed that the levels of aCL, anti-β2 GPI antibodies and LA in patients with alcoholic liver disease increased with the degree of the histological damage.
The role of aPL in cirrhotic patients is not clear, and is less likely to be pathogenic. These antibodies could reflect liver lesions and immunological dysfunction rather than true thrombotic potential [47–50].

**Portal hypertension.** Idiopathic portal hypertension has been reported also in rare instances in association with the presence of aPL [51–55]. The first case was published by Mackworth-Young et al. [51] in a patient with SLE, who also had pulmonary hypertension. Later on, Bayraktar et al. [55] reported another patient with porto-pulmonary hypertension in a patient with PAPS suggesting that microthrombi, associated with aCL as a possible cause for the occurrence of both, portal and pulmonary hypertension. In view of the few reported cases of aPL in association with portal hypertension, a causal role of these antibodies in the pathogenesis of this condition remains to be established.

**Autoimmune hepatitis.** Autoimmune hepatitis (AIH) is a disease of unknown aetiology. It is predominant among women and is characterized by hypergammaglobulinaemia, specific autoantibodies, association with human leucocyte antigens DR3 or DR4 and a favourable response to immunosuppression [56]. Specific features of the disease are its associations with several extra-hepatic immune-mediated diseases and/or syndromes [56]. However, only very few case reports on the association between AIH and the presence of aPL and/or APS have been reported so far [57–66]. In a recent study Liaskos et al. [56] studied aCL prevalence in AIH and other hepatic diseases and demonstrated a significantly higher prevalence of aCL in patients with AIH compared with other diseases and healthy people. Half of AIH patients tested positive for IgG and/or IgM aCL. aCL were associated with AIH stage, but no association was found with APS clinical manifestations (thrombosis, pregnancy morbidity, thrombocytopenia). The detection of IgG aCL in AIH patients, however, was associated with more severe disease (active disease and cirrhosis), suggesting aCL IgG as a potential additional marker of disease severity and activity. On the other hand, de Larranaga et al. [67] reported a positivity of aCL in only 3% of patients with AIH and clinical association with thrombosis. These differences could be attributed to the laboratory methods used and the design of the studies.

Could AIH develop in the context of APS? so far only one case was recently reported by Hueber et al. in a 56-year-old Caucasian female with APS who few years later developed type I AIH [68].

The presence of aPL in patients with AIH, represents most likely an immunological epiphrenomenon, as part of the hyper stimulation of the immune system and excessive antibodies production that are characteristic of this disease.

**Biliary cirrhosis.** Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases that are considered to be immune-mediated. The characteristic feature of PBC is the presence of circulating autoantibodies [69]. Only few studies with some case reports on the association between PBC or PSC and the presence of APS have been reported so far [44, 64, 70–78].

von Landenberg et al. [79] conducted a study to determine the different types of aPL (aCL, phospholipidserine (PS), and β2-GPI) in the sera of patients with PBC and AIH and control subjects. He reported that these antibodies are common in PBC patients associated with a higher level of the disease or more intense liver damage. The authors suggested IgM anti-PS antibodies as a new marker of disease activity in PBC patients [79]. In a more recent report by Zachou et al. [69], 99 PBC and 41 PSC patients in addition to normal controls were studied for the prevalence and clinical significance of aCL. IgG and/or IgM aCL were detected in 40% of PBC and PSC patients and in 2.25% of healthy individuals ($P < 0.05$). In PBC, IgG aCL was associated with presence of cirrhosis, increased Mayo risk score and thrombocytopenia, and in PSC with longer disease duration and biochemical activity. These antibodies however were found to be non-pathogenic.

aPL are frequently detected in PBC and PSC associated with a more severe hepatic disease. Although no increased thrombogenic risk associated with the presence of these antibodies has been confirmed, this potential cannot be excluded completely, and careful observation of patients with elevated levels of aPL for any signs of thrombosis is warranted.

In conclusion, purely thrombotic hepatic diseases in addition to other inflammatory and cirrhotic conditions have been reported in association with aPL. Although a cause effect relation is more established between the presence of these antibodies and thrombotic diseases of the liver, the increasing reports on the detection of aPL in non-thrombotic conditions warrants further investigation. This wide range of hepatic morbidity reflects the complex pathogenesis of this disease. There is a strong evidence so far that APS rather than being a simple thrombotic condition is a disease with a complex multifactorial aetiology involving in addition to soluble prothrombotic factors, an important role for the immune system, endothelial cells and the complement cascade [80].

**Intestinal manifestations**

Intestinal infarction has been infrequently reported in patients with aPL. Thrombosis of mesenteric vessels may result in infarction of the bowel. The presentation may be acute (acute abdomen), often preceded by intestinal angina. A number of patients have been reported with intestinal infarction from mesenteric thrombosis [81–98]. Two patients have also been documented who suffered from intestinal bleeding [99]. One patient has been reported with a giant gastric ulceration due to a widespread vascular occlusive disease involving the veins, small arteries, and arterioles of the stomach wall as well as the perigastric fat, consistent with an APS associated vasculopathy [100].

Kim et al. [95] in a study to evaluate the CT features of the abdominal manifestations of PAPS, retrospectively reviewed 14 patients who underwent abdominal CT among 32 patients who were confirmed to have PAPS. The clinical indications for abdominal CT included abdominal pain, abdominal distension, or lower leg swelling. Ten of the 14 patients had involvement of the venous system (72%), two of the arterial system (14%), and two of both systems (14%). Of the 12 patients who had venous system involvement, four had thrombosis in the inferior vena cava (IVC), two in both the IVC and the hepatic vein, one in the IVC and splenic and portal veins, one in the IVC and hepatic and adrenal veins, one in the hepatic, portal, and renal veins and three in the portal and superior mesenteric veins (SMV). Arterial thrombosis was noted in four patients, hepatic artery in two, aorta in one, renal artery in one, pancreatic arcade in one and splenic artery in one, with infarct of multiple organs including the liver, jejunum, colon, kidney and adrenal gland [95].

In a later study to determine the abdominal CT findings in patients with APS, Kaushik et al. [36] detected abdominal thromboses or ischemic events in 42 (19.5%) of 215 patients with (primary or secondary) APS. Twenty-two (52%) had major vascular thromboses, including those in the IVC ($n = 10$), portal and SMV ($n = 7$), splenic vein ($n = 4$), and aorta ($n = 1$). Thirty-six (86%) patients had abdominal visceral ischaemia resulting in renal infarction ($n = 22$), bowel ischaemia ($n = 13$), splenic infarction ($n = 6$), pancreatitis ($n = 3$), hepatic infarction ($n = 1$) and/or hepatic dysfunction with portal hypertension ($n = 1$). In some patients, more than one abdominal organ and/or vessel was involved.

In a study to determine the prevalence of celiac artery and/or superior mesenteric artery (SMA) stenosis in patients with
APS/aPL compared with healthy renal donors. Sangle et al. [101] studied 111 patients with APS (n = 57)/aPL (n = 54) and 93 healthy renal donors. Magnetic resonance angiography (MRA) was used and all patients were screened in suspended inspiration to minimize artefact from the arcuate ligament compression leading to false positive appearance of celiac artery stenosis (CAS). Thirty-nine of 111 (35.1%) patients had CAS, one had SMA stenosis and two had both, compared with the control group, 17 of 93 (18%) individuals had CAS (P < 0.01). Twenty-two of 57 (38%) APS patients had CAS, (PAPS 7/14 and secondary APS 15/43) as compared with the control group (18%) (P < 0.006). Seventeen of 54 (32%) aPL positive only group had CAS. The authors concluded that coeliac artery and SMA stenosis should be considered in APS and aPL positive patients who present with abdominal symptoms or weight loss. Furthermore, celiac axis involvement may be more frequent than previously thought. More recently Rosenthal et al. [102] reported for the first time a patient with APS and abdominal angina due to CAS, whose condition improved on prolonged anticoagulation treatment.

Venous or arterial intestinal, thromboses and infarctions seem to be prominent features of APS. The presentation may be non-specific therefore a high index of suspicion is needed for the early detection of these abnormalities. APS patients should be thoroughly investigated for any signs or symptoms suggestive of intestinal ischaemia, on the other hand patients who present with any signs of bowel ischaemia should be screened for the presence of aPL antibodies.

Splenic manifestations

Only few cases of splenic infarction associated with the presence of aPL have been reported, usually associated with occlusions of other intra-abdominal vessels such as mesenteric [14, 82] or renal [103]. More often, this feature has been described in patients presenting with CAPS [104, 105]. Autosplenectomy or functional asplenia, is a rare complication occurring in SLE. It is characterized by splenic atrophy and the demonstration of schistocytes, target cells and Howell-Jolly bodies in the peripheral blood smear [106]. Only one case of APS has been reported with this complication so far [107].

Although infrequently reported, ischaemic splenic involvement should be considered in the context of APS, especially in patients with the CAPS.

Pancreatic manifestations

A number of cases of acute pancreatitis associated with aPL have been reported [108–113]. The first case of pancreatic involvement in association with aPL was described by Bird et al. [108] in a patient with acute, severe, intravascular coagulation complicated by hepatic, pancreatic, and renal damage, and ischaemic necrosis of the extremities. The patient had LA and aCL and a history of recurrent abortions. Later on Wang et al. reported a case of SLE and APS who presented with a picture of acute pancreatitis. Post mortem autopsy of the pancreas revealed, chronic inflammation with thrombi in the pancreatic arteries, in the absence of vasculitic changes, suggesting decreased pancreatic blood flow as a possible cause of pancreatitis [109]. Chang et al. [110] also reported a case of PAPS with acute haemorrhagic pancreatitis. Yeh et al. [111] later on reported four patients with SLE and high levels of aCL who presented with acute pancreatitis. Three of the four patients succumbed. The authors suggested that acute pancreatitis and elevated aPL should be considered in patients with SLE who present with acute abdominal pain [111]. More recently Spencer [113] reported the case of a young female with PAPS and recurrent episodes of acute pancreatitis and suggested that the investigation of patients with idiopathic pancreatitis should include checking their aPL.

Acute pancreatitis should be considered in the differential diagnosis of SLE and APS patients who present with acute abdominal pain. The pathogenesis of this abnormality is not yet clear; however, preliminary autopsy reports suggests a thrombotic rather than an inflammatory aetiology.

Inflammatory bowel disease

One of us (MK) previously described the case of a young woman with recurrent thrombosis associated with aCL who went on to develop Crohn’s disease. This was the first report of an association between these two clinical conditions [114]. Since then a number of studies were published reporting a significantly higher prevalence of aPL in patients with inflammatory bowel diseases (IBD), particularly with Crohn’s disease [115–118].

The significance of aPL in IBD seems to be a non-specific immunological phenomenon and the thrombotic potential of these antibodies remains uncertain.

The catastrophic antiphospholipid syndrome

The CAPS syndrome is a very serious condition characterized by widespread thrombosis. GI ischaemia has been reported in 14–38% of patients with CAPS [119–122]. In a series of 80 patients with CAPS, 18 (22%) had abdominal pain as the presenting sign [123]. In a recent review of 250 patients with CAPS, hepatic involvement was reported in 34% of patients, bowel infarctions in 24% and splenic involvement in 18%. Involvement of the pancreas has also been reported. Intestinal involvement was documented in 30.5% of autopsies, splenic in 28.8%, and hepatic in 20.3%. Splenic infarcts were seen in 10.2% of the autopsies, hepatic infarcts in 3.3%, and BCS in 1.6%. Abdominal involvement was the cause of death in 4 (4.9%) patients (3 patients with liver failure and 1 patient with acute abdomen) [124, 125].

Necropsy findings available on 59 of the patients revealed microthrombi in 84.5% of the patients examined [125]. The presence of these microthrombi is one of the features that differentiate classic APS from CAPS. In the former, single venous or arterial occlusions of the medium-to-large blood vessels usually dominate the clinical picture. In CAPS, however, severe multiple organ dysfunction, characterized by diffuse small-vessel ischaemia and thromboses predominantly affecting the parenchymal organs, dominates [125].

In a recent large retrospective literature search, Cervera et al. [126] analysed the clinical and laboratory characteristics of 97 patients with intestinal involvement secondary to the APS (37 patients with classic APS and 60 with CAPS). The prevalence of abdominal pain as the presenting manifestation of intestinal ischaemia was higher in patients with classic APS (76 vs 37%; P < 0.005). The main difference in histopathological findings between the two groups was the higher rate of microthrombosis in patients with CAPS (75 vs 4%; P < 0.0005). The mortality rate was higher in patients with CAPS (55 vs 17%; P < 0.0005).

Abdominal involvement in CAPS is frequent, whereas in classic APS large vessel occlusions are the major causes of thrombosis, thrombotic microangiopathy seems to be the major pathogenetic mechanism in CAPS [80].

Conclusion

Liver involvement, in various forms, is the most frequent abdominal manifestation associated with APS. Acute intestinal infarction, intestinal angina and intestinal bleeding have also been reported in association with aPL in addition to few sporadic cases of splenic infarction and acute pancreatitis.

A high index of suspicion for any signs of abdominal involvement should be considered in patients with APS. In addition, screening for aPL should be carried out in patients...
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References

Abdominal manifestations of APS


