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Suprarenal gland hemorrhage: A bleeding manifestation that may be caused by thrombosis of efferent veins

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Abstract

Suprarenal gland hemorrhage has been described in several conditions (sepsis, local traumas, surgical procedures, anticoagulant therapies, ACTH administration, protracted stress, hypoxemia). The condition is rare in congenital bleeding disorders. Recently, two new morbid conditions, namely Heparin induced thrombocytopenia and Antiphosfolipids Antibodies Syndrome have been reported as frequent causes of suprarenal gland bleeding. The condition may be classified as monolateral or bilateral. The first is usually paucisymptomatic, the latter, severely symptomatic. The causative mechanisms are two, namely 1) direct congestion and damage of the gland with secondary leakage of blood and consequent cell destruction and 2) thrombosis of efferent veins with consequent upstream increased pressure and rupture of vessels. The first mechanism, direct cellular insult is typical of most of the old cases. On the contrary, the thrombotic occlusion of efferent veins is typical of the new morbid conditions, namely Heparin induced thrombocytopenia, Antiphospholipids Antibodies Syndrome and Polycythemia vera. This second mechanism could be envisaged as an example of thrombo-hemorrhagic disorder. An idiopathic form has also been described. The variety and complexity of causes have great implications in diagnostic procedures, therapeutic approaches and outcomes.

Introduction

Bleeding is usually an overt event involving skin, mucosae, body orifices. Sometimes it may be a covert one involving non-clinically visible structures such as brain, liver, spleen, endocrine glands. Contrary to other organs, such as gastrointestinal tract, lung, urinary tract, uterus, etc, which communicate with the surface of the human body through ducts or canals, the bleeding in covert organs cannot be seen. It has to be suspected on clinical signs and symptoms and then demonstrated by radiological or surgical procedures [1]. Suprarenal gland hemorrhage belongs to the covert group of bleeding and appears to be frequently underdiagnosed if it is limited to only one of the two glands [2-5].

The condition has been known for many years, but it has drawn great interest only recently since it was noted to occur in clinical entities such as Heparin Induced Thrombocytopenia (HIT) and Antiphospholipids Antibodies Syndrome (APAS) conditions, which have been defined only in the past two decades [6-18]. The purpose of the present review is to deal in a systemic way which suprarenal gland hemorrhage.

Classification, etiology and pathophysiology

A problem of Semantics has to be clarified. The suprarenal glands are often referred to as Adrenal glands. In our view this is not correct since the term "suprarenal" refers to the entire gland composed of a cortical part and of a medullary part. Adrenal strictly refers only to the medullary part where cathecholamines, including adrenalin, are secreted. Since bleeding may involve the entire gland and not only the medullary part, we think it is correct to use the term suprarenal gland. Another important aspect is the classification of the bleeding in monolateral or bilateral. This has a great importance in diagnosis and management. Finally, another classification concerns the causative mechanisms. These may be summarized in 1) local (tumor, trauma, surgery), 2) systemic (infections, ACTH stimulation, stress), 3) occlusion (thrombosis) or compression of the suprarenal veins. This is an important classification that indicates the variety and complexity of the causes. The main causes of bleeding in suprarenal glands are listed in Table 1.

Of particular interest are the cases observed after partial hepatectomy or liver transplantation. The culprit in these cases is probably trauma, surgical procedures, ligation or blood sampling of suprarenal veins [19-27]. In some cases, the bleeding has been maintained to be secondary

Table 1. Main causes of adrenal gland hemorrhage

1	Sepsis (meningococcal infection)
2	Abdominal trauma and surgery
3	Hyperstimulation with ACTH
4	Segmental hepatectomy (monolateral)
5	Liver transplantation (monolateral)
6	Hypoxic disorders (neonates)
7	Anticoagulant therapies
8	Thrombosis or occlusion of adrenal and efferent veins (Antiphospholipid antibodies syndrome, Heparin induced Thrombocytopenia, Polycythemia)
9	Coronary arteries surgical procedures
10	Persistent stressful conditions
11	Congenital coagulation disorders
12	Rupture of aneurysms or tumors (Fheochromocythoma)
13	Adrenal vein sampling
14	Idiopathic

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to thrombosis [28,29]. Since bleeding in this case may be monolateral, usually there are no important systemic symptoms and signs. The role of thrombosis in the pathogenesis of suprarenal gland bleeding is still not completely clarified. Because of the especially rich vascularization existing in the gland, it is conceivable that stasis due to vein obstruction may cause upstream increased pressure and rupture of vessels with consequent extravasation of blood. Each gland receives blood from small arteries deriving from the inferior phrenic artery, the abdominal aorta and the renal arteries [30].

These small arteries perforate the capsule and form a rich sub capsular plexus of arterioles. The arterioles irradiate along the "zona fasciculata" to the "zona reticularis" where it forms a deep plexus known as the cortico-medullary dam. This "dam" effect is due to the fact that at the passage between the "zona reticularis" and the medulla, venules show prominent bundles of smooth muscle fibers before entering the medullary vein and then into the central vein. The latter, on the right site, drains into the inferior vena cava (I.V.C.) and, on the left side, into the renal vein (RV) [30]

The role of thrombosis in the pathogenesis of suprarenal gland hemorrhage is supported also by the observation that the condition has been reported in patients with congenital thrombophilia [31]. The cases of adrenal gland bleeding after ACTH stimulation observed in clinical practice are of extreme interest. Intramuscular ACTH was widely used 20-30 years ago, now it is seldom used. It is interesting to note that most of the numerous papers dealing with ACTH induced adrenal hemorrhage appeared in that period. It has been proven even in the experimental animal that massive ACTH stimulus increased blood flow to the suprarenal glands [32-34].

Because of the rich vascularization of the gland it is feasible that extravasation may occur. The sporadic cases of adrenal hemorrhage seen in conditions of sustained stress have probably the same origin. We are aware of only one case of adrenal hemorrhage occurring in a hemophilia A patient. The patient was a neonate who showed a hematoma of the right renal gland that caused anemia, dyspnea, abdominal distention. Abdominal sonography was diagnostic. Proper substitution therapy was successful [35]. Another patient with hemophilia A had an aneurysm of an adrenal vein which was confused with a tumor [36].

Contrary to the rarity seen for congenital bleeding disorders, suprarenal gland hemorrhage has been frequently reported during anticoagulant therapy with both heparin and coumarin drugs [2,37-39]. A special form of suprarenal gland hemorrhage has been described in neonates [40,41]. Particularly predisposed are the neonate who are under ExtraCorporeal Membrane Oxygenation (ECMO) procedures [42].

An important consideration in this regard is the double role that heparin has with suprarenal gland bleeding. It can be secondary to the protracted use of intravenous heparin that cause bleeding, but it could also be the result of a Heparin induced thrombocytopenia (HIT) with consequent thrombosis of suprarenal or renal veins [9-11,28]. Sepsis was often reported in the past as a cause of suprarenal gland hemorrhage with consequent catastrophic gland failure [3,38]. Unfortunately, the event may occur even today [43].

Besides the cases that can be attributed to a specific cause, some reports refer to spontaneous or idiopathic hemorrhage. The existence of this form is not proven yet because the absence of risk or triggering conditions have not always been ruled out [44].

Diagnosis

Diagnostic suspicion of suprarenal gland bleeding may be relatively easy in case of bilateral involvement. On the contrary it may be difficulty because of non-specific clinical and laboratory manifestation, in case of monolateral bleeding. Vague abdominal pain radiating to flank, nausea, vomiting, hypotension, positive history for trauma, recent surgery, systemic conditions as HIT and APAS, are frequent findings (Table 2). From a laboratory standpoint, hypohyponatremia, hyperkalemia and increased BUN are commonest findings. The most critical diagnosis concerns the monolateral vs the bilateral bleeding. On clinical grounds monolateral forms are usually associated with trauma and surgical procedures. On the contrary bilateral or massive forms are secondary to sepsis, prolonged ACTH stimulation, HIT or APAS, namely systemic conditions (Tables 3 and 4). Sonography, CAT and/or MRI are diagnostic [3,5] (Figures 1 and 2). The CAT reveals an isointense or hypointense mass. It has to be remembered that before the introduction of imagine techniques the great majority of cases of monolateral adrenal hemorrhage were diagnosed at autopsy or during exploratory surgery [2,3,24].

Contrary to what occurs for bleeding in other endocrine glands, bleeding in a suprarenal gland and, especially in case of bilateral involvement, systemic, often acute, changes become promptly evident (lethargy, mental confusion, hypotension, severe asthenia, shock).

Management

The approach varies with the severity of the condition. Since the monolateral lesion is usually benign in evolution, surgical removal should be limited only to cases in which there is, on a CAT control, an increase in the size of the mass. Bilateral forms require prompt

Table 2. Value of signs, symptoms and recent past history in the diagnosis of suprarenal gland hemorrhage

Recent abdominal surgery, HIT, APAS, polycythemia
Abdominal pain
Back and flank pain
Chest pain
Weakness
Nausea, vomiting
Hypotension
Anorexia
Fever
Abdominal rigidity and rebound
Mental confusion
Hypothermia
Shock

Table 3. Pathogenetic mechanisms of suprarenal gland hemorrhage

1. Primitive or direct damage	2. Secondary damage due to thrombosis of efferent veins	3. Idiopathic
Sepsis	HIT	
ACTH administration	APAS	
Hypoxemia (neonate)	Congenital thrombophilia	
Local trauma or surgery	Polycythemia	

Table 4. Differential diagnosis of types of Suprarenal hemorrhage

Monolateral	Bilateral
Often asymptomatic,or paucisymptomatic	Always clearly symptomatic
Often an incidental report	Sepsis
Complication of kidney surgery	HIT, APAS
Complication of gall bladder surgery	ACTH administration

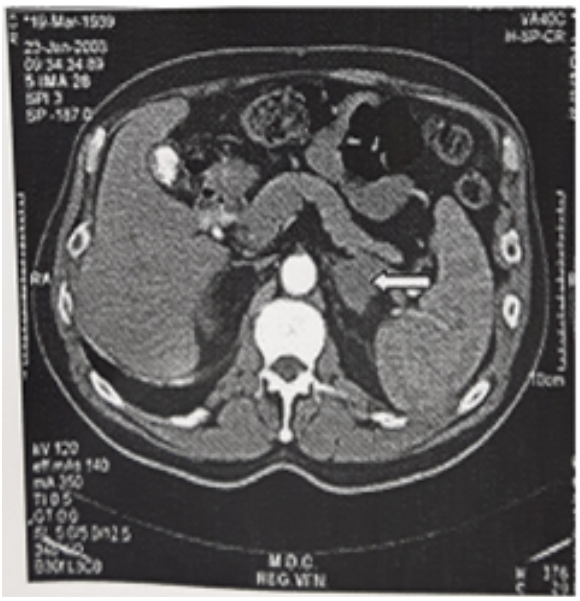

Figure 1. CAT image of a left-side suprarenal gland hemorrhage. Enlarged gland is indicated by an arrow. The patient had Antiphospholipid antibodies syndrome (APAS) and showed a recovery

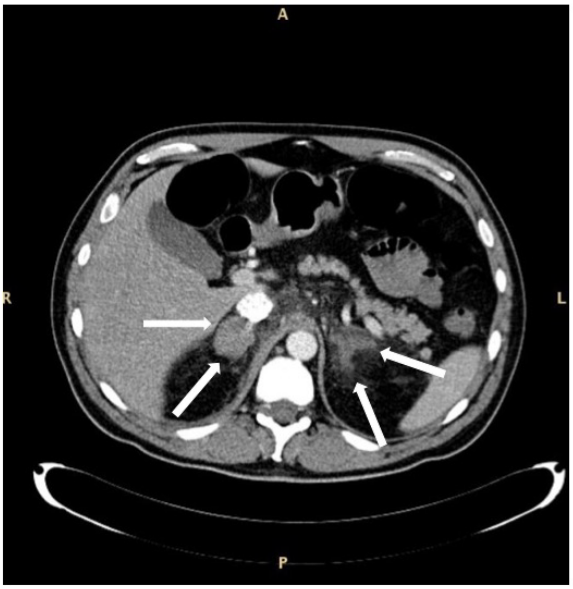

Figure 2. CAT of a bilateral suprarenal gland hemorrhage in a patient with sepsis and myelodysplastic syndrome with excess blasts type 1. The enlarged glands are indicated by arrows. The aspect of the right gland appears more uniform as compared with that of the left one. Patient survived

administration of cortisone and strict ions surveillance. Blood pressure should be maintained with plasma expanders and fluids. Specific measures may be required in certain cases (for example, antibiotics in case of sepsis).

Prognosis

Prognosis is variable, depending on the extension of the involvement, monolateral or bilateral. Monolateral involvement has usually a good prognosis even without therapy but for patients with clotting disorders. Bilateral, massive hemorrhage is an acute, serious event associated in the past with frequent fatalities. Recent diagnostic procedures as CAT or MRI have allowed a prompt diagnosis thereby improving the prognosis. Fatalities are now rare.

Conclusions

The first observation on Suprarenal Glands bleeding refers to the rarity of the event among congenital bleeding disorders. Only one patient with Hemophilia A has been reported [35].

This is more so when one considers that these patients are at present time frequently investigated by CAT or MRI. It is likely that minor suprarenal grand hemorrhages in patients with congenital clotting factor deficiency go undetected because of the most important overt bleeding manifestations (hematuria, hematomas, hemarthrosis, gastro-intestinal bleeding) seen in these patients. On the contrary, anticoagulant therapy may be associated with suprarenal gland bleeding. Both heparin and coumarin drugs have been implicated [37-39]. However, it has to be remembered that an important cause of suprarenal gland bleeding is rupture of small arteries or capillaries secondary to impairment in blood flow due to thrombotic obstructions in the adrenal veins. Since thrombosis is exceptional in congenital bleeding disorders [45,46], this could also explain the rarity of suprarenal gland bleeding in congenital coagulation disorders.

This paucity of observation may indicate that the pathogenesis of suprarenal gland bleeding is often due to thrombotic occlusion of the central vein with upstream stasis and bleeding due to rupture of small arterial vessels. This is what occurs in the present-day cases of suprarenal gland hemorrhage due to HIT and APAS. Post-surgery or post-trauma cases are probably due to direct damage to venous and arterial vessels without stasis due to vein occlusions. In the old cases due to adrenal hyperstimulation secondary to ACTH administration, a direct damage to cells was involved. The same direct damage was also involved in the premature, hypoxic newborn during the attempt at oxygenation therapy [40,42].

It is interesting to note that pathogenetic mechanism may be varied but the result is the same, namely destruction of gland tissue with consequent failure. The bleeding may involve different areas of the gland (cortex or medulla) with consequent discrepant decrease of hormones. Since the main action of suprarenal gland hormones (aldosterone, adrenalin, etc) control blood pressure, their deficiency causes hypotension and shock. That may be acute, subacute or chronic according to the rate and degree of adrenal damage. The recent cases observed during HIT or APAS and due to thrombotic occlusion of the adrenal veins with consequent upstream stasis and congestion have received the interest of clinicians. It is important today, in the contest of these immunological syndromes, to pay due attention to abdominal signs and symptoms and flank pain, nausea, vomiting, hypotension, weakness. In the presence of any of these signs and symptoms, a radiological investigation of the suprarenal glands is absolutely indicated.

Even the cases observed in Polycythemia are probably due to impaired venous drainage or thrombosis due to the hyperviscosity of blood [29]. The role carried out by venous obstructions is a new pathogenetic element in the study and management of suprarenal gland hemorrhage. Physicians caring for patients with HIT or APAS should be alert about the possibility that such conditions could be responsible for suprarenal gland bleeding. It is likely that even the so called idiopathic cases of suprarenal gland hemorrhage [44] might represent unrecognized cases due to thrombosis.

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