

Bilateral adrenal hemorrhage

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ABSTRACT

Bilateral adrenal hemorrhage represents a challenging condition which requires multi-modal intervention. Our aim to systematically review the published cases diagnosed with this condition. The method we used is based on PubMed database research. The papers are published between 2005 and 2020. We included articles that follow the subsections: idiopathic type, hemorrhage in patients with adrenal tumors, in subjects with hematologic diseases, with autoimmune/systemic conditions, in COVID-19 positive patients, in subjects using anticoagulants, respective in pregnant females.

Keywords: adrenal, hemorrhage, infarct, adrenal tumor, bilateral adrenal tumor, pregnancy, anticoagulant

INTRODUCTION

Bilateral adrenal hemorrhage represents a challenging condition which requires multi-modal intervention. Our aim to review the published cases with this condition. The method we used is based on PubMed database research. The papers are published between 2005 and 2020.

IDIOPATHIC BILATERAL ADRENAL HEMORRHAGE

Idiopathic bilateral adrenal hemorrhage is bleeding in the absence of any known adrenal pathology and without any predisposing factors or caused at diagnostic or during follow-up (1,2,3). Several cases have been published in the literature. For instance, Ogino et al. reported a case of idiopathic bilateral adrenal hemorrhage of a 54-year old female (1). Computed tomogra-

phy (CT) of the abdomen showed left adrenal hemorrhage (2.5x4.2x4.2 cm) and additional right adrenal hemorrhage (2 x 3.6 x 3.4 cm); laboratory investigation released low cortisol levels thus early glucocorticoid replacement therapy was initiated; after one month the patient was discharged (1). Antón et al. published a case of bilateral adrenal hemorrhage, the patient was 80-year old female; predisposing factors were excluded, therefore was diagnosed as spontaneous idiopathic BAH; CT scan of the abdomen showed a bilateral adrenal hemorrhage, enlarged adrenal glands 6.5x5.5 cm (left) and 6x5 cm (right); the patient recovered after the introduction of glucocorticoid replacement therapy (2). Another case was published by Song et al. – this is a 50-year old female who had a spontaneous regression of idiopathic bilateral adrenal hemorrhage (3). Dahiya et al. reported a 46-year old male who was identified with the condition based on autopsy exam (4) (see Table 1).

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BILATERAL ADRENAL HEMORRHAGE IN ADRENAL TUMORS

Ali et al. published a retrospective study (between 2012 and 2018) on 11 patients that were included; they presented with non-traumatic acute adrenal hemorrhage in Sheffield Teaching Hospitals; adrenal glands were evaluated based on CT scan (5). Women were 63.6%; median age was 58 (27-89) years; patients was initially treated without surgery, but after a median of 10 weeks, 5 patients underwent adrenalectomy (pathological examination showed 2 benign, 2 malignant and 1 necrotic tumor) (5). Most of the patients with adrenal hemorrhage had as predisposing factors adrenal tumors and anticoagulant therapy (5). Liu et al. published the case of a 52-year old male with giant bilateral adrenal hemorrhagic myelolipomas as showed by CT with post-operative confirmation (6). The adrenal metastases from non-small cell lung carcinoma (NSCLC) were identified in one case published by Hiroi et al.: this is a 56-year old male, with CT lesions of 5.9x4.2 cm of left and 6x4 cm of right mass (7). Surgery was not performed because the patient had also bone metastases (7) (see Table 1).

BILATERAL ADRENAL HEMORRHAGE IN HEMATOLOGIC DISORDERS

Myeloproliferative disease increases the risk of thrombo-haemorrhagic events, for instance, a case of bilateral adrenal hemorrhage was published by Mendoza et al., a 71-year female with acute myeloid leukemia, and thrombocytopenia (8). Manganaro et al. published a case of a 65-year old male, with myelodysplastic syndrome, admitted at the emergency room with: acute epigastric pain, vomit, nausea and dyspnea (9). Uminski et al. described a 55-year old female case with myelofibrosis and additional bilateral adrenal hemorrhage demonstrated by CT; laboratory tests showed thrombocytopenia, without evidence of adrenal insufficiency (10). Bhandari et al. described a case of bilateral adrenal hemorrhage on a 64-year old man with polycythemia vera who was admitted for hypotension, tachycardia, hypoglycemia and elevated coagulation parameters; CT showed bilateral adrenal hemorrhage (right adrenal gland of 5.3x3.4x3.8 cm and a left adrenal gland of 6.1x4.3x5.4 cm) (11). Gönen et al. published the case of a 56-year old man who was confirmed with bilateral adrenal hemorrhage and polycythemia; CT showed a right, respective left adrenal gland mass of 4x5x5.5 cm, respective 4x3x2 cm (12) (see Table 1).

BILATERAL ADRENAL HEMORRHAGE IN AUTOIMMUNE/SYSTEMIC CONDITIONS

Antiphospholipid syndrome (APLS) is a pro-thrombotic autoimmune disorder and it is a major risk factor for adrenal hemorrhage (13). Ramon et al. published a retrospective study between 1990 and 2010 on 23 patients with bilateral adrenal hemorrhage secondary to APLS; only 16 patients survived the acute phase; median follow-up of patients was 3.5 years (range 0.3-28.1); median age of adrenal failure was 33.5 years; the adrenal insufficiency was irreversible in majority of patients (13). Aldaajani et al. published a case of bilateral adrenal hemorrhage after discontinuation of warfarin therapy; the patient was a 43-year old male with medical history of APLS secondary to systemic lupus erythematosus; clinical presentation and laboratory examination were consistent with adrenal insufficiency; bilateral adrenal thrombosis lead to hemorrhage and it was confirmed on CT scan (14). Minami et al. reported a case of a 56-year old male with history of follicular non-Hodgkin lymphoma and APLS during the development of chronic Graf-versus-host disease complicated by bilateral adrenal hemorrhage (15). Also, Potter et al. presented a case of 57-year old female with medical history of several episodes of thrombosis in addition to adrenal condition and APLS (16). Adrenal hemorrhage is associated with stress caused by sepsis, classically with fulminant meningococemia (Waterhouse-Friderichsen syndrome); sepsis increasing the risk for adrenal hemorrhage (17). Guarner et al. published a postmortem study on 65 patients with bacterial infections in different tissues, a study between 1998 and 2006 in Centers for Disease Control and Prevention (17). Adrenal glands were evaluated with hematoxylin and eosin stains, the hemorrhage was found in 39 patients (60%) of 65 cases (17). *Neisseria meningitidis* was the bacteria most frequently associated with adrenal hemorrhage (17). Stojanović et al. described a case of 20-year old male who died and on autopsy revealed hemorrhage in many organs even bilateral adrenal hemorrhage with Waterhouse-Friderichsen syndrome (18). Godfrey et al. published a case of bilateral adrenal hemorrhage with many risk factors for this entity: AFLP, postoperative state, anticoagulant therapy and sepsis (19). Khwaja J. published a case of bilateral adrenal hemorrhage due to urosepsis of *Escherichia coli* (20). Hale et al. described the case of a 36-year female with of Waterhouse-Friderichsen syndrome caused by *Streptococcus pneumoniae*; massive adrenal hemorrhage was confirmed at autopsy (21). Hiroi et al. presented one case of an elderly female patient with acute adrenal insufficiency following a septic shock with *Klebsiella pneumoniae* (22) (see Table 1).

TABLE 1. Papers that introduce cases with bilateral adrenal hemorrhage: PubMed database, between 2005 and 2020

Name	Year	Age/sex	Type of study/ number of patients	Adrenal pathology	Condition predisposing to adrenal hemorrhage
Zinserling et al.	2020 (23)	-	Retrospective postmortem study/10	Bilateral adrenal hemorrhage	COVID-19
Freire Santana et al.	2020 (24)	F/M = 2/10 Age [34-38]	Retrospective postmortem study/12	Bilateral adrenal hemorrhage	COVID-19
Leyendecker et al.	2020 (25)	M/F = 3/1 Mean age 67 +/-11 [42-88]	Retrospective study/219	Bilateral adrenal hemorrhage	COVID-19
Álvarez-Troncoso et al.	2020 (26)	70/M	Case report/1	Bilateral adrenal hemorrhage	COVID-19
Frankel et al.	2020 (27)	66/F	Case report/1	Bilateral adrenal hemorrhage	COVID-19 Antiphospholipid syndrome
Houlden et al.	2020 (29)	69/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state- total hip arthroplasty Anticoagulant therapy-Dalteparin Thrombocytopenia
Jensen et al.	2020 (31)	68/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-knee surgery Anticoagulant therapy-heparin Infection Thrombocytopenia
Windsor et al.	2020 (47)	76/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-femur fracture Anticoagulant therapy -Dalteparin
Tan et al.	2020 (37)	63/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-subtotal colectomy Heparin-induced thrombocytopenia (HIT)
Arosemena et al.	2020 (48)	46/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid Syndrome Anticoagulant therapy-rivaroxaban
Mendoza et al.	2019 (8)	71/F	Case report/1	Bilateral adrenal hemorrhage	Acute myeloid leukemia- Thrombocytopenia
VanderVeer et al.	2019 (28)	68/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-knee arthroplasty Heparin-induced thrombocytopenia (HIT)
Alidoost et al.	2019 (49)	68/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-knee arthroplasty Anticoagulant therapy- rivaroxaban
Tedjaseputra et al.	2019 (50)	83/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-total hip replacement Anticoagulant therapy-heparin
Montealegre-Gallegos et al.	2019 (38)	72/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-coronary artery bypass surgery Heparin-induced thrombocytopenia (HIT)
Pereira et al.	2019 (51)	65/M	Case report/1	Bilateral adrenal hemorrhage	Sepsis
Ducoux et al.	2019 (52)	31/F 19/M	Case report/2	Bilateral adrenal hemorrhage	Myelofibrosis Thrombocytopenia
Ali et al.	2018 (5)	F/M = 7/4 Mean age = 58 [27-89] years	Retrospective study/11	1-Phaeochromocytoma 1-Adrenal metastasis 1-Neurilemmoma 1-Hyperplasia 1-Adrenal neoplasm Bilateral adrenal hemorrhage	Tumor pathology Anticoagulant therapy (2 on rivaroxaban and 2 on warfarin)
Uminski et al.	2018 (10)	55/F	Case report/1	Bilateral adrenal hemorrhage	Myelofibrosis -Thrombocytopenia

Name	Year	Age/sex	Type of study/ number of patients	Adrenal pathology	Condition predisposing to adrenal hemorrhage
Aldaaani et al.	2018 (14)	43/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Systemic lupus erythematosus Thrombocytopenia
Senthikumar et al.	2018 (53)	28/M	Case report/1	Bilateral adrenal hemorrhage	Russell's Viper Envenomation- vasculotoxic effects
Fatima et al.	2018 (54)	47/M	Case report/1	Bilateral adrenal hemorrhage	Sepsis
Jonnalagadda et al.	2017 (46)	26/F	Case report/1	Bilateral adrenal hemorrhage	Pregnancy
Minami et al.	2017 (15)	56/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Thrombocytopenia Anticoagulant therapy-warfarin
Khawaja J.	2017 (20)	49/F	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Anticoagulant therapy-warfarin Urosepsis Thrombocytopenia
Heitz et al.	2017 (55)	53/M	Case report/1	Bilateral adrenal hemorrhage	Waterhouse-Friderichsen syndrome during Varicella Zoster infection Anticoagulant therapy
Serafino et al.	2017 (42)	76/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative stress- pancreaticoduodenectomy
Song et al.	2016 (3)	50/F	Case report/1	Bilateral adrenal hemorrhage	Idiopathic
Liu et al.	2016 (6)	52/M	Case report/1	Bilateral myelolipomas Bilateral adrenal hemorrhage	Expansion of tumor was a trigger for necrosis
Bhandari et al.	2016 (11)	64/M	Case report/1	Bilateral adrenal hemorrhage	Polycythemia vera Elevated coagulation parameters
Fralick et al.	2016 (56)	65/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Anticoagulant therapy-rivaroxaban
Cho et al.	2016 (33)	50/M	Case report/1	Bilateral adrenal hemorrhage	Anticoagulant therapy -warfarin
Hale et al.	2016 (21)	36/F	Case report/1	Bilateral adrenal hemorrhage	Sepsis Waterhouse-Friderichsen syndrome Purpura fulminans
Nazir et al.	2016 (57)	62/F	Case report/1	Bilateral adrenal hemorrhage	Idiopathic
Potter et al.	2015 (16)	57/F	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Anticoagulant therapy-enoxaparin Thrombocytopenia
Mudenha et al.	2015 (58)	75/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-hip replacement surgery Anticoagulant therapy -warfarin
Ilunakhamhe et al.	2015 (40)	64/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-T-12 laminectomy Heparin-induced thrombocytopenia (HIT)
McGowan-Smyth S.	2014 (34)	77/M	Case report/1	Bilateral adrenal hemorrhage	Anticoagulant therapy -warfarin
Godfrey et al.	2014 (19)	68/F	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid Syndrome Postoperative state-total hip replacement Anticoagulant therapy-warfarin Septic shock

Name	Year	Age/sex	Type of study/ number of patients	Adrenal pathology	Condition predisposing to adrenal hemorrhage
Gowda et al.	2014 (59)	40/M	Case report/1	Bilateral adrenal hemorrhage	Sepsis Anticoagulant therapy-warfarin
Tattersall et al.	2014 (60)	61/M	Case report/1	Bilateral adrenal hemorrhage	Heparin-induced thrombocytopenia (HIT) Sepsis
Gelisse et al.	2014 (61)	63/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid syndrome Heparin-induced thrombocytopenia (HIT) Sepsis
Ramon et al	2013 (13)	F/M = 9/7 33.5 years (10.7-48.4)	Retrospective study/16	Bilateral adrenal hemorrhage	Antiphospholipid syndrome
Ogino et al.	2013 (1)	54/F	Case report/1	Bilateral adrenal hemorrhage	Idiopathic
Manganaro et al.	2013 (9)	65/M	Case report/1	Bilateral adrenal hemorrhage	Myelodysplastic syndrome Thrombocytopenia
Stojanović et al.	2013(18)	20/M	Case report/1	Bilateral adrenal hemorrhage	Waterhouse-Friderichsen syndrome Sepsis
Best et al.	2013 (62)	75/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-hip replacement Anticoagulant therapy-dabigadran Sepsis
Dahiya et al.	2012 (4)	46/M	Case report/1	Bilateral adrenal hemorrhage	Idiopathic
Thota et al.	2012 (36)	68/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-knee arthroplasty Heparin-induced thrombocytopenia (HIT) Anticoagulant therapy-warfarin
Bharucha et al.	2012 (63)	84/M	Case report/1	Bilateral adrenal hemorrhage	Antiphospholipid Syndrome Anticoagulant therapy-warfarin Cellulitis
Bockorny et al.	2012 (45)	27/F	Case report/1	Bilateral adrenal hemorrhage	Pregnancy
Gönen et al.	2011(12)	56/M	Case report/1	Bilateral adrenal hemorrhage	Polycythemia Vera Thrombocytosis
Kallinen et al.	2011(44)		Postmortem Retrospective study	Bilateral adrenal hemorrhage	Burns
Peel et al.	2011 (64)	60/M	Case report/1	Bilateral adrenal hemorrhage	Surgical stress-hemicolectomy
Stern et al.	2010 (65)	54/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-lobectomy for the lung cancer Antiphospholipid Syndrome Anticoagulant therapy-Fandoparinux
Sezer et al.	2010 (43)	51/M	Case report/1	Bilateral adrenal hemorrhage	Surgical stress- coronary bypass
Antón et al.	2009 (2)	80/F	Case report/1	Bilateral adrenal hemorrhage	Idiopathic
Egan et al.	2009 (66)	81/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-hemicolectomy Sepsis
Corsini et al.	2009 (67)	63/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-hemicolectomy
Rajamanickam et al.	2009 (68)	52/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-total knee arthroplasty Anticoagulant therapy-enoxiparin

Name	Year	Age/sex	Type of study/ number of patients	Adrenal pathology	Condition predisposing to adrenal hemorrhage
Guarner et al.	2008 (17)	-	Retrospective study/65	Bilateral adrenal hemorrhage	Bacterial infections
Picolos et al.	2007 (32)	68/M	Case report/1	Bilateral adrenal hemorrhage	Anticoagulant therapy -warfarin
Joseph et al.	2007 (39)	70/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-hemicolecotomy Heparin-induced thrombocytopenia (HIT)
Pianta et al.	2007 (41)	38/M	Case report/1	Bilateral adrenal hemorrhage	Stress induced by acute pancreatitis
Hiroi et al.	2006 (7)	56/M	Case report/1	Bilateral adrenal metastases from lung adenocarcinoma	Expansion of adrenal metastases may induce hemorrhage of the tumors
Lykissas et al.	2006 (30)	83/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-total hip replacement Anticoagulant therapy- Fandoparinux
Hiroi et al.	2005 (22)	77/F	Case report/1	Bilateral adrenal hemorrhage	Sepsis
Schuchmann et al.	2005 (69)	83/F	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-total knee arthroplasty Anticoagulant therapy-heparin
Bakaeen et al.	2005 (70)	52/M	Case report/1	Bilateral adrenal hemorrhage	Postoperative state-coronary artery bypass surgery Heparin-induced thrombocytopenia (HIT)

BILATERAL ADRENAL HEMORRHAGE AND COVID-19

Adrenal tissue have a high vulnerability in patients affected by COVID-19 due to the presence of virus receptors at the level of adrenal glands (23-27) (see Table 1).

BILATERAL ADRENAL HEMORRHAGE AND ANTICOAGULANT USE

Bilateral adrenal hemorrhage is most often associated with use of an anticoagulant (28,29,30). Vanderveer et al. reported a case of a patient 68-year old male with acute adrenal insufficiency caused by bilateral adrenal hemorrhage whilst on anticoagulant (rivaroxaban 10 mg) following knee arthroplasty (28). Houlden et al. published a similar due to dalteparin 5000 UI post total hip arthroplasty; few days after surgery she was admitted on hospital with abdominal pain due to adrenal insufficiency; CT showed bilateral adrenal masses (3.5 cm left, 3.6 cm right) (29). Lykissas et al. described the case of a 83-year old female who developed bilateral adrenal hemorrhage first day after surgery for total hip replacement during anticoagulant therapy with fandoparinux 2.5 mg (30). Jensen et al. published a case of a 68-year old female with multi-factorial panel: stress induced by the recent surgery, anti-

coagulant therapy and infection; CT confirmed bilateral adrenal hemorrhage (right 2.7x1.6 cm, left 3.2x2.1 cm) (31). Also, patients treated for atrial fibrillation with warfarin may develop bilateral adrenal hemorrhage (32,33,34). The condition may be related to HIT (heparin-induced thrombocytopenia) (35-40). Chow et al. reported a case of adrenal failure secondary to bilateral adrenal hemorrhage following orthopedic surgery stress (35). Thota el al. published a case of 68-year old man who underwent knee surgery; warfarin was utilized to prevent deep venous thrombosis (36) (see Table 1).

BILATERAL ADRENAL HEMORRHAGE AND STRESS

Stress can induced adrenal hemorrhage; adrenaline can induced platelets aggregation, turbulence and vasoconstriction that may lead to hemorrhage (41,42). Pianta et al. published a case of 38-year old male with acute pancreatitis who developed large bilateral adrenal hemorrhage on CT scan (41). Serafino et al. reported a case of 76-year old female with bilateral adrenal hemorrhage after pancreaticoduodenectomy for a malignant ampulloma (42). Sezer et al. introduced a similar case after coronary bypass surgery (43). Kallinen et al. published a postmortem retrospective study on 71

patients with severe burns who died between 1995 and 2005 in Helsinki Burn Centre, and 4 patients had adrenal hemorrhage (3-bilateral adrenal hemorrhage, 1-unilateral adrenal hemorrhage); the cause of death was multiple organ failure (44) (see Table 1).

BILATERAL ADRENAL HEMORRHAGE AND PREGNANCY

Pregnancy is a known, yet very rare, risk factor for adrenal hemorrhage; pregnancy is associated with adrenal cortex hyperplasia and hypertrophy, which may predispose to venous congestion and hemorrhage (45,46) (see Table 1).

DISCUSSIONS

Adrenal hemorrhage represents a condition accompanying local (adrenal) diseases or systemic diseases (71,72). Its recognition is essential since glucocorticoids replacement is lifesaving (73,74). The level of statistical evidence is dominated by case reports rather than vast studies (1-70).

CONCLUSION

The importance of recognition a severe condition as bilateral adrenal hemorrhage is based on the fact that multiple medical and surgical practitioners relate to it.

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