A CASE SERIES OF SPONTANEOUS EXTRAPERITONEAL HEMORRHAGE IN COVID-19 PATIENTS IN MALAYSIA

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ABSTRACT

Background: COVID-19 infection is associated with thrombotic events causing micro thrombosis and venous thromboembolism. Anticoagulant treatment has been shown to reduce mortality in COVID-19 cases and is routinely used. Spontaneous extraperitoneal hemorrhage (SEH), which includes retroperitoneal, iliopsoas or rectus sheath hematomas, is a known complication of anticoagulant use. Trans arterial embolization (TAE) is a safe and minimally invasive management option to control bleeding in SEH. We report 7 cases of SEH in COVID-19 patients admitted to Hospital Sungai Buloh. This case series highlights the occurrence of SEH in COVID-19 patients, its clinical and radiological manifestations and management pathways.

Case presentation: All patients were on anticoagulants and presented with abdominal pain and/or swelling with sudden drop in hemoglobin. Computed tomography angiography (CTA) showed contrast extravasation indicative of active bleed. All patients proceeded with conventional transfemoral angiography with option of TAE. TAE was utilized in 6 out of 7 cases and was successful in achieving hemostasis with no procedure related complication.

Conclusion: SEH should be suspected in COVID-19 patients on anticoagulants presenting with abdominal pain or drop in hemoglobin. CTA is confirmatory and TAE offers a viable and safe treatment option.

Keywords: COVID-19, extraperitoneal hemorrhage, embolization

INTRODUCTION

The COVID-19 pandemic continues to cause unprecedented challenges to the health system. Involvement of the hematological system in COVID-19, principally thrombotic events causing micro thrombosis and venous thromboembolism has been widely written in the medical literature (1–3).

Anticoagulant treatment has been shown to reduce mortality and as such, it is routinely used in large number of COVID-19 cases (2,4). However, the liberal use of anticoagulants has its disadvantages. Spontaneous extraperitoneal hemorrhage (SEH) is a known complication of anticoagulant use (5). It includes retroperitoneal, iliopsoas or rectus sheath hematomas irrespective of cause and is increasingly being reported in COVID-19 patients (6–10).

Trans arterial embolization (TAE) allows superselective embolization of small-vessel bleeding points at various sites. It is a safe and minimally invasive management option to control bleeding of arterial origin usually seen in SEH.

Table 1. Clinical characteristics, laboratory values at time of bleeding, management and outcome of patients

Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age (years)	75	55	58	64	75	62	53
Sex	Male	Male	Male	Male	Male	Female	Female
Existing disease	DM, HTN, HLP	CRF, DM, HTN	CRF, DM, HTN	HTN	No known medical illness	Chronic Hepatitis B, HLP, endometrial carcinoma	DM, HTN, bronchial asthma
COVID category	4	4	4	5 *	4	5	4
Day of COVID 19 diagnosis when SEH suspected	17	11	11	15	11	4	15
Day of enoxaparin treatment when SEH suspected	7	6	4	10	7	3	5
CTA findings	Right retroperitoneal hematoma	Left retroperitoneal hematoma	Bilateral rectus sheath hematoma	Left rectus sheath and left iliacus hematoma	Pelvic and rectus sheath hematoma	Bilateral rectus sheath hematoma	Left rectus sheath hematoma
Embolized artery	Right L3 and L4 lumbar arteries	Left L3 and L4 lumbar artery	Empiric embolization of bilateral inferior epigastric artery	Branch of left internal iliac artery	Nil (no contrast blush on angiography)	Right lateral circumflex femoral artery	Bilateral inferior epigastric artery
Hemodialysis	-	2, 4, 6	2, 4, 6	-	-	-	-
Anticoagulant	Enoxaparin (treatment dose)	Enoxaparin (prophylaxis dose)	Enoxaparin (prophylaxis dose)	Enoxaparin (treatment dose)	Enoxaparin (treatment dose)	Enoxaparin (treatment dose)	Enoxaparin (treatment dose)
Hb (g/dL)	5.1	5.5	6.2	7.9	6.8	6.0	5.6
PLT ($x10^9$/L)	364	285	282	202	342	259	283
PT (INR)	1.52	1.16	0.94	1.09	1.09	1.03	1.06
APTT (sec)	50.4	46.0	42.0	36.6	29.1	53.4	49.1
Embolic agent	Coil	Gelatin sponge	Gelatin sponge	Gelatin sponge	Nil	Coil	Coil
Signs and symptom during bleeding	Abdominal pain and swelling	Abdominal pain and swelling	Abdominal swelling	Abdominal swelling	Abdominal pain and swelling	Abdominal pain and swelling, hypovolemic shock	Abdominal pain and swelling, hypovolemic shock
Outcome at day 30 post embolization	Death	Survived	Death	Death	Survived	Death	Survived

CASE PRESENTATION

We experienced 7 patients with COVID-19 infection confirmed to have SEH in between April 2021 to September 2021, at the height of Malaysia's third wave of COVID-19 cases.

Patient's past medical histories, blood investigation before angiography, signs and symptoms during bleeding, imaging findings, bleeding vessel and management pathways were collected and summarised in Table 1.

APTT: activated partial thromboplastin time, CRF: chronic renal failure, CTA: computed tomography angiography, DIVC: disseminated intravascular coagulation, DM: diabetes mellitus, Hb: hemoglobin, HLP: hyperlipidemia, HTN: hypertension, PC: packed cell, PLT: platelets, PT(INR): prothrombin time (international normalized ratio), *: intubated prior to bleeding

Patients age ranged from 53 to 75 years (average 63 years). None of these patients had prior hematologic disease or were on regular antiplatelet or anticoagulant therapy. Two patients were on regular hemodialysis.

Four patients were in category 4 (symptomatic, pneumonia requiring supplemental oxygen) and 2 patients were in category 5 (critically ill with multi-organ involvement). All the patients received enoxaparin (2 on prophylaxis dose and 5 on treatment dose). Four patients had pulmonary embolism confirmed on CT pulmonary angiogram. Prior to these bleeding events, 6 patients required supplemental oxygen therapy with non-invasive ventilation and 1 patient required invasive ventilation.

The mean number of days from initial COVID-19 diagnosis to the development of SEH was 12 days (range 4 – 17 days). The mean number of days of the development of SEH from the commencement of enoxaparin in the 7 patients was 6 days (range 3 – 10 days). Clinical diagnosis of SEH was suspected when patients had abdominal pain and/or swelling with abrupt drop in hemoglobin. All the patients underwent urgent CTA followed by conventional angiography within 24 hours of suspected SEH. Two patients developed hypovolemic shock.

Prior to angiography, the hemoglobin ranged from 5.1-7.9g/dL (average 6.2g/dL), platelet count ranged from 202-364x109/L (average 288x109/L), prothrombin time (international normalized ratio) ranged from 0.94-1.52 (average 1.12) and activated partial thromboplastin time ranged from 29.1-53.4s (average 43.8s).

SEH was diagnosed by computed tomography angiography (CTA), which showed contrast extravasation indicative of active bleed. No vessel malformations were found. Four patients had rectus sheath hematoma, 2 patients had retroperitoneal hematoma and 1 patient had both rectus sheath and retroperitoneal hematoma.

Every patient went for conventional transfemoral angiography. Bleeding vessels were identified in 5 patients with good agreement to CTA findings (Figs 1A, B, 2A, B, C). Three patients showed bleeding points from more than one artery. A single type of embolic agent was used in each case. Hemostasis was achieved in 2 patients using gelatin sponge and 3 patients using coils. In 2 patients bleeding was not identified on conventional angiography; 1 had empiric embolization with gelatin sponge and 1 was managed conservatively based on CTA findings and clinical condition. One interventional radiologist performed all 6 embolization procedures. There were no complications. None underwent surgery.

Each of the 6 patients who had TAE required a single embolization intervention to achieve hemostasis. TAE was successful in stabilizing the hemoglobin level at 24 hours for all patients. Two patients were alive at 30 days after embolization. Despite the technical success of embolization, four patients died within 30 days after embolization. These 4 deaths were probably unrelated to TAE due to the absence of signs of hypovolemic circulatory collapse prior to their deaths.

DISCUSSION

SEH is a serious event which requires urgent investigation and management. It carries a mortality rate ranging from 20-30% (5,11–13). Its risk factors include use of anticoagulants, age over 65 years, end stage renal failure, hemodialysis, heart failure, hepatic insufficiency, coagulation disorders and higher COVID-19 categories (6–9,12,14,15). Our set of patients similarly had these risk factors. One study of COVID-19 patients showed an incidence of 1.8% of major spontaneous hemorrhage in patients on prophylactic low molecular weight heparin, as

opposed to 0.5% in general hospitalized patient (16,17). Another study showed an overall bleeding rate of 4.8% with major bleeding rate of 2.3%, most of whom were anticoagulated (3). Coughing and positive pressure ventilation, both common in COVID-19 patients, may cause raised intra-abdominal pressure leading to possible vessel rupture. The systemic cytokine storm which occurs in COVID-19 infection may also cause endothelial cell dysfunction and abnormal platelet recruitment, which increases the propensity to bleed (1,18).

SEH commonly present as hypotension, abdominal pain/swelling or drop in hemoglobin (5–8). Clinical symptoms and signs of SEH may not be apparent until a bleeding patient has suffered substantial blood loss. Therefore a high index of vigilance for SEH is necessary in COVID-19 patients on anticoagulation by close monitoring of vital signs and serial hemoglobin estimates. Signs of hypovolemia, anemia and symptoms abdominal or flank pain should raise the suspicion of hemorrhage. CTA should be promptly performed to diagnose these non-overt SEH. Active bleed on CTA is seen as contrast extravasation with increased pooling on delayed phase. CTA has up to 87% sensitivity in detecting active bleed in good agreement with angiographic findings (13,19–21).

Immediate management should include supportive measures such as fluid resuscitation, blood transfusion and cessation/reversal of anticoagulant to optimize coagulation status (22). Management options for SEH are conservative treatment, TAE or surgery. Medical management is possible if patient is hemodynamically stable, relatively small hematomas with no evidence of active bleed on CT and patients not requiring repeated transfusion (23). Lucatelli et al. experience with SEH in 21 patients with COVID-19 showed most patients who were on conservative management had to be referred for angiography after median of 2 days due to persistent drop in hemoglobin (24).

In active bleeding, conservative management can be unsuccessful needing urgent timely intervention (13,19,22). TAE is a safe and effective method in treating SEH with a low rate of complications (12,13,15,20). Surgery is reserved for failure of conservative management, in patients with persistent bleeding despite radiologic TAE, and in the development of abdominal compartment syndrome (22). TAE has had significant success in stopping further SEH bleeding including in this case series, although in few cases needing repeat session (7,9,23,24). A study of 21 COVID-19 patients with spontaneous bleed treated with TAE showed overall survival rate of 70% at 30 days (23). Our survival rate of 33% was lower than in the literature, likely to be related to the severity of their COVID-19 categories, co-morbidities and our small sample size. We observed that none of the patients had further significant drop in hemoglobin post embolization and prior to death.

The most common arteries involved in SEH are the inferior epigastric artery and deep circumflex artery in abdominal wall bleeding, and the lumbar arteries in retroperitoneal bleed (13). More specific to COVID-19, the typical bleeding pattern seen is of multiple foci of bleeding involving distal branches, as seen in 3 of our patients (16) (Fig. 2B). It is prudent to catheterize all the arteries of the same anatomic territory of the hematoma to locate other bleeding arteries or anastomosis (Figs. 2B, C). Some patients may show contrast extravasation in CTA but negative findings in conventional angiography (11). One reason may be due to the higher sensitivity of CTA in identifying contrast extravasation compared to conventional angiography. CTA is capable of detecting bleeding at rate of 0.3-0.5mLs/min as opposed to conventional angiography at rate 0.5-1.0mls/min (25,26). Other reasons include intermittent bleed, spasm, hypotension or soft tissue tamponade. Therefore, empirical embolization of possibly involved arteries may control occult bleeding (14,21,24). Re-bleeding is more often due to delay in correction of abnormal coagulation profile or involvement of different artery/territory (11,13,21).

Evidence for best embolic material for TAE in SEH is lacking. Taking into consideration the bleeding pattern usually seen in COVID-19, the use of small sized polyvinyl alcohol particles were utilized in superselective embolization of the entire arterial segment related to the bleeding (27). This allows distribution of embolic material to the most distal branches. Coil is preferred in embolizing larger diameter single vessel or feeding vessel (28). Its disadvantage is incomplete occlusion in presence of collaterals, commonly seen in rectus sheath hematomas. Gelatin sponge is a temporary embolic

agent with relatively distal target embolization, used in smaller targeted vessels or empirical embolization. However, the embolized arteries recanalize between 3 weeks to 4 months, which may cause re-bleeding (29). Combination of gelatin sponge and coil embolization may be used if either agent does not stop the bleeding vessel on its own (12). The recurrence rate of SEH was found to be similar between resorbable and non-resorbable embolic material (13). Our case series demonstrated technical success in the use of either coil or gelatin sponge to stop the bleeding. Liquid embolic agents such as N-butyl cyanoacrylate glue has also been used successfully for embolization of SEH in COVID-19 patient (24). It is fast acting, permanent and its effect does not depend on coagulation process hence useful in coagulopathic patients. However, it requires extensive operator experience and superselective cannulation of bleeding branches to prevent non-target embolization (30).

Limited literature is available as to when to reinitiate anticoagulants after SEH, especially in COVID-19 patients with concurrent deep venous thrombosis or pulmonary embolism. One study of 15 non COVID-19 patients with retroperitoneal hemorrhage showed out of 12 patients who survived, 4 patients restarted anticoagulation after a withdrawal period of 4-25 days without further complications (5).

CONCLUSION

SEH is a potentially lethal complication of COVID-19 infection, especially in the elderly on anticoagulation. A high index of suspicion is needed in patients with abdominal pain and decline in hemoglobin level. Failure of conservative management, hypovolemic shock or presence of active bleed on CTA warrants treatment with TAE.

STATEMENT OF ETHICS

This study has been granted an exemption from requiring ethics approval from Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-21-02091-K8G (IIR).

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

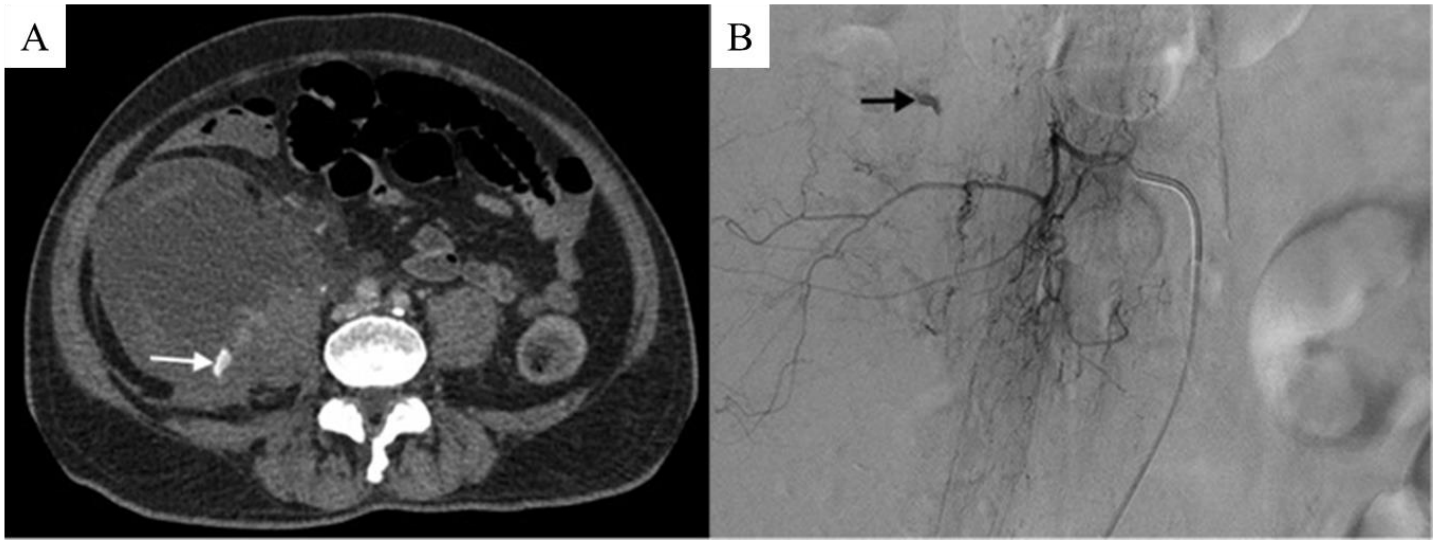

Figure 1: Images from a 75 year-old with retroperitoneal hematoma (patient 1). (A) Computed tomography angiography shows large right retroperitoneal hematoma with contrast extravasation (white arrow). (B) Digital subtraction angiographic image shows extravasation from branch of right L3 lumbar artery (black arrow).

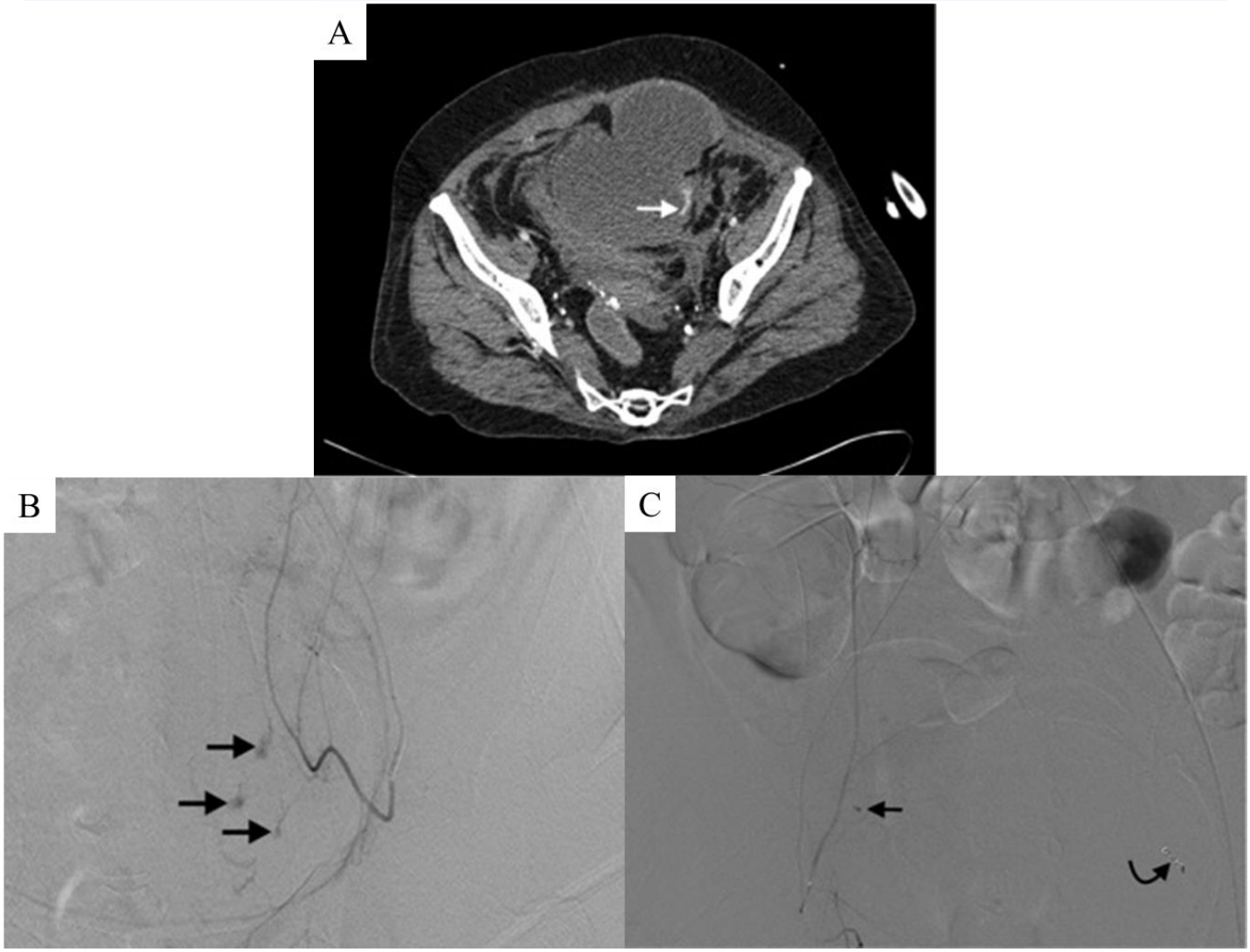

Figure 2: Images from a 53 year-old with left rectus sheath hematoma (patient 7). (A) Large rectus sheath hematoma with contrast extravasation (white arrow). (B) Digital subtraction angiographic image showing multiple bleeding points from left inferior epigastric artery (black arrow). (C) Digital subtraction angiographic image showing bleeding point from right inferior epigastric artery (black arrow) and coiled left inferior epigastric artery (curved black arrow).