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Case reports

Systemic lupus erythematosus and antineutrophil cytoplasmic antibodies-associated vasculitis overlap in an elderly woman: A case-based literature review

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ABSTRACT

Background: The overlap of systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody (ANCA) associated-vasculitis (AAV) is a rare entity. *Aim of the work*. To report a rare case of overlap SLE and AAV complicated by small bowel perforations and nephritis.
Case presentation: An 81-years-old Chinese woman presented with a two-weeks history of progressive bilateral lower limb weakness and dysuria. An incidental uterine mass was found, and a total hysterectomy was performed with extensive small bowel adhesion and multiple enteric perforations discovered intra-operatively. SLE was diagnosed based on the presence of cutaneous vasculitis, positive antinuclear antibody, anti-double stranded deoxyribonucleic acid, consumed complements, thrombocytopenia, nephritis, and pleural effusion. Positive perinuclear-ANCA and histological findings of the resected small bowel led to evidence of co-existing AAV. Hence, these findings have led to a diagnosis of overlap SLE and microscopic polyangiitis (MPA). The patient received daily hydroxychloroquine (200 mg), azathioprine (50 mg) followed by intravenous (IV) hydrocortisone (200 mg/8 h) and cyclophosphamide (750 mg/m^2). The patient's condition deteriorated with respiratory failure and hypotension and was eventually intubated and ventilated. IV immunoglobulin (4 mg/kg/day) was given for 3 days with resolution of the vasculitic lesions. The renal function rapidly declined with hemodynamic and clinical deterioration and the patient died.
Conclusion: This case demonstrates the diagnostic conundrum and complexity in the management of a late presentation of an overlap syndrome with rare life-threatening complications. To our knowledge, this is the first case diagnosed and managed in Malaysia and the oldest patient diagnosed with overlap SLE/AAV in the literature.

1. Introduction

An overlap of systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibodies- (ANCA-) associated vasculitis (AAV) is an extremely rare entity [1]. Both conditions have distinct clinical features and demographic characteristic despite sharing a similar organ system involvement. The prevalence of overlap SLE and AAV was low [2,3]. The commonly encountered overlap AAV phenotype was glomerulonephritis (GN) associated with rheumatoid arthritis [2]. Perinuclear ANCA is notably present in 15 – 20% of lupus patient [4]. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome) [5].

The presence of vasculitis is a well-documented phenomenon in patients with SLE. In one study vasculitis was reported at a frequency of 35.9% in SLE patients [6]. The role of ANCA vasculitis in lupus is unclear and yet to be elucidated. Nephritis in both SLE and AAV (small vessel) can be distinguished by histopathological findings. GN in lupus nephritis (LN) is characterised by presence of glomerular immune deposits, whereas in AAV it's typically characterised by sclerotic changes (necrotizing and crescentic GN)

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without significant immune deposition [7]. Gastrointestinal involvement in vasculitis, though uncommon, may present with a variety of clinical manifestations ranging from mild to serious complications [8]. Intestinal perforation is a rare but life-threatening complication of AAV and is usually associated with GPA or MPA [9–11]. Ongoing studies to decipher and understand the pathogenesis of this condition may improve the prognosis.

Herein, we present an elderly woman who presented with multiple small bowel perforation with glomerulonephritis complicating SLE and AAV overlap. Both entities fulfilled the 2019 American College of Rheumatology (ACR) classification criteria for SLE [12], and 2012 Chapel Hill International Consensus on Vasculitis (CHCC) [5], respectively. The phenotypic involvement pattern of pulmonary, renal, cutaneous and gastrointestinal tract was consistent with MPA as described in previous study [13]. The latter manifestation is, however, rare. The diagnosis is further supported by the presence of MPO-ANCA. A late presentation combined with a delayed diagnosis and treatment, leads to poor or fatal outcome in this threatening condition.

2. Case report

An 81-year-old Chinese woman with no available past history, presented with bilateral lower limb weakness and dysuria for 2 weeks duration. Apart from findings of a pelvic mass, the magnetic resonance imaging (MRI) showed a prolapsed intervertebral disc without evidence of spinal stenosis or cauda equina syndrome. Coronavirus 2019 (COVID-19) polymerase-chain-reaction (PCR) screening was negative.

The patient underwent a total abdominal hysterectomy, and bilateral salphingo-oophorectomy (TAHBSO). Histopathological examination (HPE) revealed adenomyosis uteri and benign adenomyoma of the myometrium. There was no evidence of endometrial hyperplasia or malignancy. Open laparotomy was ensued following intraoperative findings of extensive small bowel adhesions with multiple perforation in which a small bowel resection was performed. HPE of the small bowel showed extensive area of hemorrhage with transmural inflammation of the bowel wall. However, no immunofluorescence study was performed. Despite resection, persistent leakage was noted from the operative wound. A second laparotomy was not pursued due to hypotension with oliguria. The patient was transferred to the intensive care unit (ICU) and was commenced on intravenous (IV) methylprednisolone 250 mg daily for 3 days (based on a working diagnosis of a medium-vessel vasculitis). She responded well to the treatment. A second laparotomy was subsequently attempted, and an upper proximal small bowel perforation was discovered. Despite being repaired without further bowel resection done, there was persistent leakage from the wound. Hence, due to this combined with poor oral intake, total parenteral nutrition (TPN) was administered. *E. coli* and *Klebsiella* were isolated from the surgical wound which was an extended-spectrum beta-lactamase (ESBL) type. Intravenous (IV) sulperazone was commenced from which she demonstrated good clinical improvement. Despite this improvement, she continued to experience intermittent fever and developed multiple purpuric vesicular skin lesion on both foot and lower limbs (Fig. 1A and B). The HPE from skin biopsy was consistent with bullous vasculitis (Fig. 1C–E). In view of this, IV methylprednisolone 250 mg daily was given for another 3 days.

Laboratory investigation revealed positive anti-nuclear antibody (ANA) with a titre of 1:2560 (homogenous pattern), anti-dsDNA antibody (enzyme-linked immunosorbent assay, ELISA) levels of 324.7 IU/mL, low complement 3 (C3) 0.68 g/L and low normal C4 (0.1 g/L). The extractable nuclear antigens (ENA) (anti-SSA, SSB, URNP, Jo1 and Sm antibodies) were negative. Perinuclear-ANCA (p-ANCA) was qualitatively positive. The anti-myeloperoxidase (MPO) antibodies were moderately raised (42 U/mL) and anti-PR3 was negative. The immunoglobulin (IgA, IgM, IgG) levels were normal. The activated prothrombin time (aPTT) was prolonged. However, the venereal disease research laboratory (VDRL), viral hepatitis screening (HBsAg and anti HAV antibody) and the screening for antiphospholipid antibody syndrome (APS) (lupus anti-coagulant, and anti-cardiolipin antibodies) were negative. Urinalysis revealed persistent hemo-proteinuria (red blood cells >500 cells/L; white cells >250 cells/L), but no casts were detected. Urinary protein was 2+ on a dipstick. The direct antiglobulin test (DAT) was negative. The complete blood count revealed a hemoglobin of 9.9 g/dl, RBC 2.45 $x10^{12}$/L, white cell counts 4.9×10^{9}/L with lymphopenia (14%), MCV 110 fl and platelet count of 566 $x10^{9}$/L (subsequent platelet count drop to a range of 50–70×10^{9}/L). The ESR and C-reactive protein were 65 mm/1st hour and 23 mg/dL, respectively. Serum albumin was 34 g/L, serum creatinine 67 μmol/L and urea 6 mmol/L. Procalcitonin level was not done due to unavailability of the test.

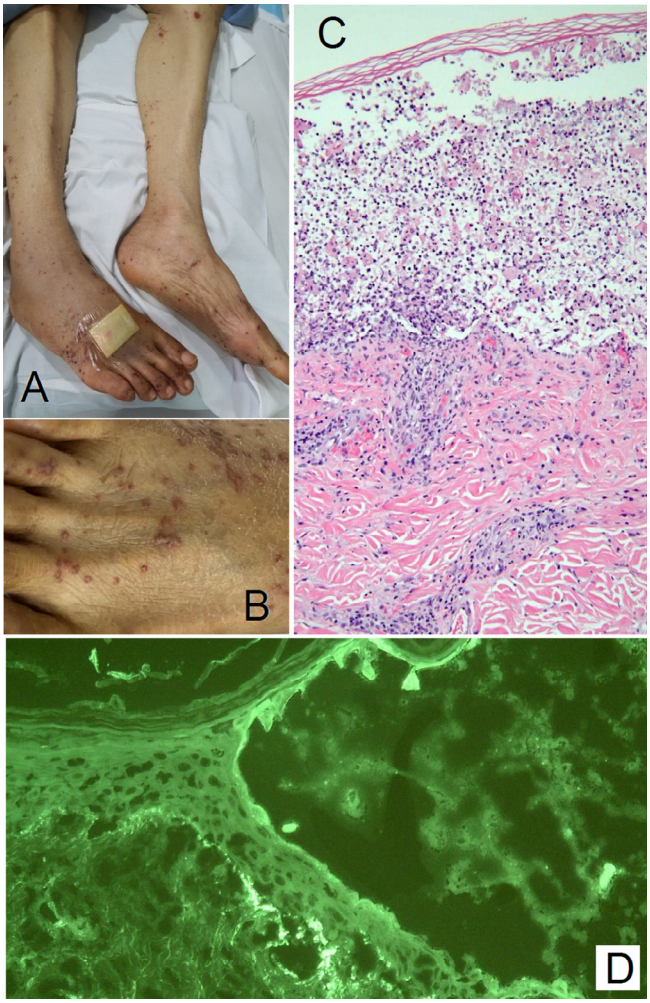

Fig. 1. Purpuric skin lesion on both lower limbs (A) and magnified image of vesicles and purpura (B). Histopathological examination showed subepidemal bullae with marked neutrophil infiltration with necrotic epidermis. The epidermal-dermal junction is infiltrated by eosinophils, neutrophils and occasional lympho-plasmacytic cells. Superficial perivascular is infiltrated by mixed inflammatory cells predominantly eosinophils; extensive fibrinoid necrosis and thrombosis at the superficial dermis, (C). The immunofluorescence study showed positivity of IgG, IgA, IgM and C3 for vessels and epidermal-dermal junction (D).

Computed tomography (CT) of the abdomen postoperatively showed hyperdense and thickened small intestinal and urinary

bladder walls suggestive of extensive inflammation. High resolution CT (HRCT) chest revealed a collapsed of the right upper lobe, ground glass opacity with mild fibrotic changes at the periphery and bases. Bilateral pleural effusions were noted (left more than right) (Fig. 2).

Oral hydroxychloroquine 200 mg daily and oral azathioprine 50 mg daily were added followed by IV hydrocortisone 200 mg 8 hourly and IV cyclophosphamide 750 mg/m^2. The patient's condition however, deteriorated with respiratory failure and hypotension. She was eventually intubated and ventilated. A repeat pulse of IV methylprednisolone 500 mg daily for 3 days was given and was followed by IV hydrocortisone 100 mg 8 hourly. IV immunoglobulin 4 mg/kg/day was then given for 3 days with resolution of the vasculitic lesions on both legs and foot. The patient was extubated successfully and remained hemodynamically stable after 4 days ICU. The repeat urinalysis revealed persistent active cellular sediments (raised erythrocytes and leukocytes) with proteinuria (>250 and >500, 2 – 3+, respectively). The 24-hour urine protein was 0.61gm. The eGFR however, rapidly declined over a few days accompanied by oliguria. Due to cost concerns, IV rituximab (RTX) was not initiated.

Subsequently, bleeding was noted from another location in the surgical wound causing hemodynamic instability with drop of hemoglobin level (from 9 to 5.5 gm/L). Her platelet count was 3×10^9/L at this stage (most likely due to disseminated intravascular coagulation). She was commenced on inotropes. Fresh frozen plasma, cryoprecipitate and packed red cells were transfused. Major exploratory laparotomy was not amenable since the patient was critically ill. IV methylprednisolone 500 mg daily was reinstated. Continuous venovenous haemodialysis (CVVH) was planned but unfortunately was not pursued due to her rapid hemodynamic and clinical deterioration. The patient finally succumbed to the illness.

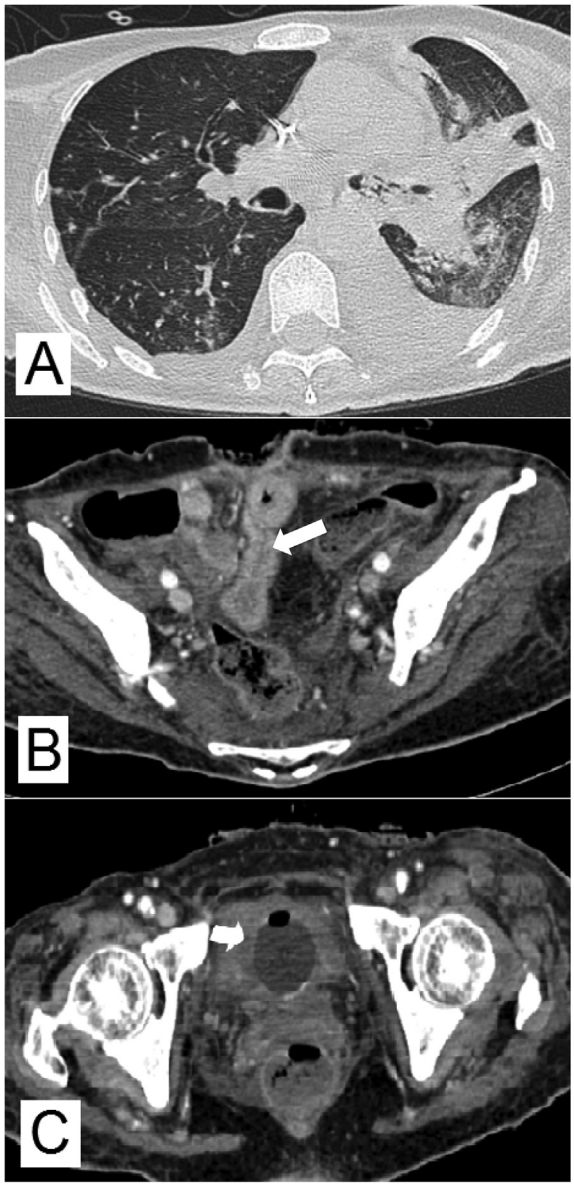

Fig. 2. High resolution computed tomography of the chest axial view showing left upper lobe collapse, bilateral pleural effusion, and ground glass opacity with peripheral fibrosis (A). Contrast enhanced computed tomography of the abdomen showing hyperdense and thickened small intestines wall (arrow) (B) and bladder wall is diffusely thickened (arrow) (C).

3. Discussion

Overlap SLE/AAV is extremely rare and commonly occur in the young age group. The oldest patient reported was 77-year-old [14]. To our knowledge, patients diagnosed over the age of 80 have not been reported in the literature. Intra-operative findings of multiple small bowel perforation prompted the autoimmune disease work-up in this patient. Positive serological markers (ANA, anti-dsDNA antibodies, low C3, thrombocytopenia, presence of bullous vasculitis) in our case fulfilled the 2019 ACR Classification Criteria for SLE [12]. Bowel perforation is uncommon in SLE and may be life threatening. It's usually caused by lupus mesenteric vasculitis which leads to bowel infarction [15]. The prevalence of lupus mesenteric vasculitis has been reported to be 2.2–9.7% in Asia [16]. However, the overwhelming and widespread vasculitis with marked inflammatory changes involving the small bowel, urinary bladder but sparing the kidney (as evidenced from the CT scan) is a rare manifestation of SLE. Bowel perforation may occur even before diagnosis of SLE being apparent and established [17].

ANCA-associated vasculitides are rare heterogenous autoimmune diseases which causes necrotizing vasculitis. There are three established histological categories: GPA, EGPA and MPA [5]. Although this classification based on the size of the predominant vessels involved (large, medium, and small), the symptoms can overlap. Gastrointestinal manifestation of these diseases is uncommon (most often medium and small vessels involvement) and usually presents in the advanced stages of the disease. The symptoms may vary from non-specific to serious complications, such as bowel perforation due to ischemia and ulceration [18]. Based on the histological findings of the resected bowel and positive p-ANCA in the present case, the 2012 revised CHCC nomenclature for a systemic vasculitis [5] was fulfilled. MPA was considered in our case based on the CHCC classification, raised MPO and multisystemic involvement: cutaneous (purpura), pulmonary (ILD), renal (nephritis) and gastrointestinal manifestations. *Gayraud et al.* reported that GI manifestations occur in 30 – 56% of MPA patients [19] in contrast with study by *Pagnoux et al.* [8].

In general, both SLE and AAV share common organ system involvement, such as arthritis, cutaneous lesions (vasculitis), cytopenia, and nephritis. They may be distinguished by distinct clinical manifestations, demographic profile, serology, and histopathological changes. SLE has been reported in most cases preceded AAV of various clinical phenotypes in the range of months to years (Table 1) [14,20–24]. AAV is usually suspected when the patient develops life threatening complications. Nevertheless, characteristic histopathological findings with serological evidence may help to delineate both conditions apart. In a study

Table 1
Case reports of patient with overlap systemic lupus erythematosus (SLE) and ANCA-associated Vasculitis (AAV).

Study	Country	Age (y)/sex	Clinical presentation	Serology	Systemic involvement	Treatment	Outcome
Xu et al[14]	China	77; M	Dyspnea, PE, anemia	ANA, dsDNA: +ve cANCA: +ve MPO-ANCA/PR-3: -ve	*Renal*: sclerotic glomerulus, fibro-cellular and cellular crescent.	CYC, MP, IVIg, PLPH, AZA, P	Survived
Itikyala et al [20]	United State	45; F	Upper abdominal pain, heart burn, arthralgia, leukocytoclastic vasculitis	Complements: normal. ANA, dsDNA: +ve cANCA: +ve PR-3: +ve; MPO ab: -ve	*GIT*: NNG inflammation/ulcer *Lungs*: necrotic masses *Renal*: LN class V	P, CYC RTX, AZA	Survived
Curtiss et al [21]	United State	40; F	SAH, ARF, macular eruption	ANA: +ve MPO-ANCA: +ve Anti-RNP: +ve	*Renal*: pauci-immune Crescentic/necrotizing GN.	P, CYC, HCQ, AZA, RTX, PLPH	Survived
Hounoki et al [22]	Japan	35; F	Purpura, polyarthralgia, ARF	ANA, dsDNA: +ve Low C3/C4 SSA, SSB: +ve, p-ANCA: +ve	*Renal*: ANCA-associated GN	MP, P, CYC Mizoribine, TAC	Survived
Frey et al[23]	United State	69; F	Dyspnea, pleuritic chest pain, arthralgia, ARF, PE	ANA, dsDNA: +ve ACL, LAC ab: +ve p-ANCA: ± ve MPO/PR-3: -ve.	*Renal*: focal necrotizing GN	P, CYC, AZA, dialysis	Died
Meyler et al [24]	United State	26; M	Dyspnea, asthenia, PE, hemoptysis, fever, edema,	ANA, dsDNA + ve; Low C3/C4 p-ANCA: +ve, PR-3: -ve	*Renal*: focal, necrotizing and crescentic GN, with LN class V	MP, CYC, PLPH	Survived
This study	Malaysia	80; F	Asthenia, lower limb weakness, bullous/leukocytoclastic Vasculitis LLs, PE	ANA, dsDNA + ve, Low C3 p-ANCA: +ve, PR-3:-ve Anti-Jo 1/Ro52: +ve	*GIT*: perforated small bowel *Lungs*: GGO, PE, fibrosis/collapse upper lobe *Renal*: GN	MP, AZA, HCQ, CYC, IVIg	Died

F, female; M, male; +ve: positive; -ve: negative; ANCA, anti-neutrophilic cytoplasmic antibody; c-ANCA, cytoplasmic ANCA; p-ANCA, perinuclear ANCA; MPO, myeloperoxidase; PR-3, proteinase-3; ANA, antinuclear antibody; dsDNA, double stranded deoxyribonucleic antibody; RNP, ribonucleic protein; ACL, anti-cardiolipin antibody; LAC, lupus anti-coagulant; ARF, acute renal failure; C3, complement 3; C4, complement 4; SAH, subarachnoid haemorrhage; GN, glomerulonephritis; LN, lupus nephritis; NNG: non-necrotizing granulomatous; PE, pleural effusion; LLs: lower limbs, GGO, ground glass opacity; MP, methylprednisolone; P, prednisolone; RTX, rituximab; CYC, cyclophosphamide; AZA, azathioprine; HCQ, hydroxychloroquine; TAC, tacrolimus; IVIg, intravenous immunoglobulin; PLPH, plasmapheresis.

on the frequencies of vasculitic syndromes, vasculitis associated with SLE was present in 14.8% [25] and similarly in another study on SLE patients, vasculitis was present in 14.3% [26]. In SLE patients, cutaneous vasculitis was found to be closely related to hypocomplementemia, lupus nephritis, musculoskeletal manifestations and Sjögren syndrome [27]. In this case, SLE was diagnosed based on presence of vasculitis, positive serology (ANA and anti-dsDNA antibodies), hypo-complementemia (C3 and C4) and thrombocytopenia. Curiously, this patient presented in the advanced stage of the disease with no gastrointestinal symptom retrieved from the history. The extensive inflammation due to vasculitis from both conditions especially the AAV, resulted in deleterious complications in this patient.

Small bowel perforation in SLE, AAV or overlap cases are potentially lethal if there is delay in diagnosis and treatment [28,29]. A study by *Kronzer et al* revealed that vasculitis induced bowel perforation has a predilection for the small bowel and has a higher mortality compared to the general population [29]. The outcome of the vasculitis is poor in the presence of catastrophic gastrointestinal complications [8].

Necrotizing GN is common in both MPA and LN and are likely to co-exist in this patient. In the absence of a renal biopsy, the presence of GN can be inferred from the persistent hemo-proteinuria and sterile pyuria (in the absence of trauma). In later stages, the eGFR of this patient declined possibly due to rapid progressive glomerulonephritis (RPGN) potentiated by underlying sepsis and ongoing vasculitis which was refractory to the active management given. A study by *Jarrot et al*. revealed that the majority patients with p-ANCA (anti MPO- antibodies) and positive ANA, presents with biopsy-proven RPGN (either LN or pauci-immune GN) [30]. A renal biopsy (to support the clinical evidence of nephritis) was not performed in our patient due to her critical state of illness.

Early aggressive management with immune-suppressants showed favourable outcome albeit variable responses. High dose corticosteroid is the mainstay of therapy and combination with other immunosuppressants such as cyclophosphamide, mycophenolate mofetil, and azathioprine has been used for remission induction in non-life threatening and renal AAV with variable response. RTX was found to be effective for gastrointestinal vasculitis in SLE refractory to other immunosuppressants [20]. Whilst in severe and relapsing GPA and MPA and in most uncomplicated cases of overlap SLE/AAV especially patient with GN, induction of remission with RTX has shown a favourable outcome [21,31–34].

In conclusion, presence of vasculitis in patient with SLE should prompt clinician to consider AAV by utilising serological (ANCA) and histopathological studies. Hence, appropriate treatment regime could be instituted early, which may improve the prognosis. This patient's manifestation is extremely rare (older age, extensive bowel perforations and RPGN) due to overlap SLE and AAV. Her disease was also refractory to conventional immunosuppressants, corticosteroid, IVIg as well as surgical intervention. Further studies are required to assess if monoclonal antibodies such as RTX or other small-molecular drugs would be effective in the management of such patient. However, it would be reasonably challenging, considering the rarity of such life-threatening presentations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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