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General Medicine

VASCULITIS AND ITS VARIOUS PRESENTATIONS: A CASE SERIES

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ABSTRACT Vasculitis involves a wide spectrum of clinicopathological process with reactive damage to the involved blood vessels. There is loss of vessel integrity instigating haemorrhage & luminal compromise leading to ischemia and necrosis of the tissue supplied by the involved vessels. It may affect varied size and type of blood vessels at different locations. This case series include three cases of vasculitis affecting different organs with varied presentations. Biopsies of three patients with unusual presentations were studied. Their complete history, physical examinations, laboratory investigations including serology were analysed and clinically correlated. The patients presented with different duration of symptoms varying from as short as 1-week days to 6 weeks. Skin lesions were present in two cases. Serology and autoimmune disease markers were negative in all cases except CD56 seen in 10% of plasma in first case, ANA + was seen in second case and Weakly positive Mi-2 and borderline positive Scl-70 antibodies was seen in third case. Elevated CRP, CRP were seen in all cases. However, pathological features were in concordance with the clinical diagnosis of vasculitis. They were further classified as vasculitis mimicking multiple myeloma, Vasculitis with gastrointestinal manifestation and Henochschonlein purpura. Vasculitis though a rare disease may manifest as an acute or chronic condition. It needs timely diagnosis by clinicopathological examination to aid in further management. It is important to assess the clinical severity in primary and secondary vasculitis, as it determines morbidity and mortality.

KEYWORDS : Vasculitis, Clinico-pathological process, Henous Schonlein Purpura, Multiple myeloma

INTRODUCTION

The vasculitis is characterized by spontaneous damage to mural architecture due to presence of inflammatory leukocytes in vessel walls. It leads to bleeding as a result of insult to vessel integrity and subsequent tissue ischemia and necrosis secondary to compromise of the lumen. It may occur as an initial process or may be due to another underlying disease (autoimmune disease) or can be associated with other precipitants such as drugs, infections or malignancy affecting vessels of different size, type and location. The precise pathogenetic mechanisms triggering these diseases are undetermined. They are often austere and at times grave requiring prompt cognizance and treatment. The disease manifestation depends on the organ involved which in turn depends on the type of vasculitis [1].

The 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides (CHCC 2012) [2] reflects advances in understanding vasculitis since the 1994 CHCC. One of the most frequently affected organs in vasculitis is the skin. Patients who present in a way like systemic vasculitides are termed vasculitis mimics. It is important to exclude these causes clinically before any classification criteria are applied [3].

CASE STUDY

This case series highlights the varied manifestation of cutaneous vasculitis. Biopsies of three patients with unusual presentations were studied. Their complete history, physical examinations, laboratory investigations including serology were analysed and clinically correlated.

Table 1: Characteristics of patients

	Case 1	Case 2	Case 3
Age	72 years	47 years	35 years
Sex	Male	Male	Male
Symptoms	Fever, generalized myalgia, headache, fatigue, weight loss, multiple joint pain, bilateral shoulder pain	Fever Loose stools Mild abdomen pain Joint pain	Right lower abdomen Vomiting
Duration	6 weeks	1 week	1 week
Skin lesions	-	Occasional skin rashes	Erythematous lesions on bilateral lower limbs
Lab investigations	Anaemia Eosinophilia Raised ESR, CRP, ALP	Anaemia Elevated CRP, ferritin, ASO titre, procalcitonin	Elevated CRP, Bilirubin, ALP
Autoimmune workup	CD56 seen in 10% of plasma Elevated Beta-2-Microglobulin, IgG, IgA	ANA +	Weakly positive Mi-2 and borderline positive Scl-70 antibodies
Diagnosis	Vasculitis mimicking multiple myeloma	Vasculitis with gastrointestinal manifestation	Henous Schonlein Purpura

CASE 1: VASCULITIS MIMICKING MULTIPLE MYELOMA

A 72-year-old male, farmer, with complaints of intermittent fever for 6 weeks. Fever was associated with generalized myalgia, headache, and easy fatigability. He also complained of loss of appetite, weight loss, multiple joint pain, and bilateral shoulder pain. He was a known case of hypothyroidism on regular medication and was operated on for trigeminal neuralgia previously. Blood investigation showed, complete blood count showed decreased in Haemoglobin (Hb) (8.5 g%), red blood cells (3.3 million/cumm) and normal total count and platelets. The differential count showed mildly elevated eosinophils (11%). Peripheral smear showed, normocytic normochromic anaemia with eosinophilia was seen. There was marked elevation of erythrocyte sedimentation rate (ESR) (130 mm/hour) and C-reactive protein (CRP) (80.72 mg/L) along with elevated Alkaline phosphatase (ALP) (151 U/L) while serum calcium levels were found to be normal. Iron profile showed decreased iron (14.5 mcg/dL), total iron binding capacity (TIBC) (169 mcg/d) and transferrin saturation (8.6%).

Malaria antigen rapid test and typhidot IgM tests were negative. The renal panel, lipid profile, and stool routine were normal. Urine and blood culture and sensitivity showed no growth. Bence Jones protein and antinuclear antibody test (ANA) were also found to be negative. The liver function test showed mildly decreased serum albumin (3.1 g/dL). Rhythm abnormality was noted during 2D ECHO along with LVH, mildly dilated right atrium, good LV systolic function (EF 50-55%), and no pulmonary embolism, clots, or vegetations.

The patient underwent bone marrow aspiration and biopsy which showed moderately hypercellular marrow with trilineage hemopoiesis and moderate plasmacytosis (27%), with the presence of both mature

and immature plasma cells. CD56 (nuclear cell adhesion molecule) expression was also seen in 10% of plasma cells, leading to consider the possibility of an evolving plasma cell dyskaryosis. Gastritis changes were noted in upper gastrointestinal (GI) endoscopy and further biopsies were obtained which were suggestive of Chronic gastritis with Helicobacter pylori. No significant abnormalities were seen on ultrasonography of the abdomen and colonoscopy. Radiographs of the skull, spine, and pelvis with bilateral hips were also normal.

CXR deformed contour of left scapula (Concern of old fracture). Serum protein electrophoresis was done and showed no monoclonal band; however, the pattern was suggestive of chronic inflammatory disease. Beta-2-Microglobulin was elevated (2896ng/ml), along with elevated serum IgG and IgA at 2091 mg/dl and 410 mg/dl respectively while IgM remained normal. PET-CT showed FDG uptake in the aorta, subclavian, and common iliac/femoral arteries which were suggestive of vasculitis. Mildly FDG avid sub-centimeter supraclavicular nodes were seen, likely inflammatory in nature. There were no significant hypermetabolic or lytic lesions visualized in bones or elsewhere in the body. The clinico-pathologic spectrum was suggestive of vasculitis mimicking multiple myeloma. Thus, patient presented with features suggestive of multiple myeloma. Plasmacytosis seen in bone marrow study led us to further strongly believe that this was a case of multiple myeloma. However, CRAB criteria suggested by the international myeloma working group [4], were not met. Since the bone survey did not show any lytic lesions, the decision was made to carry out a PET CT in an attempt to visualize any hypermetabolic lesions in the bones, but we were not expecting to see features of vasculitis. Up on the newfound evidence, a diagnosis of Giant cell arteritis was made according to the American College of Rheumatology 1990 criteria. Patient responded well to steroid therapy and has remained symptom free throughout the follow up.

CASE 2: VASCULITIS WITH GASTROINTESTINAL MANIFESTATION

A 47-year-old male was presented with high-grade fever for 1 week associated with chills with on and off watery loose stools and mild pain abdomen. He also complained of occasional melena, skin rashes, and joint pain for the previous 4 to 5 months. He experienced similar episodes 4 years back and was evaluated elsewhere with no available records for the same. He was diagnosed with type 2 Diabetes Mellitus. Complete Blood count showed decreased Hb (10.4 g/dl) with normal total counts and platelet counts. Differential counts showed neutrophilia (90%) and Lymphocytopenia (4%). His liver and renal function tests were normal except for an increased gamma-glutamyl transpeptidase of 79 U/L. Serum iron (30.5 mcg/dl) and transferrin saturation (15.8%) were decreased with significant elevation in Ferritin (8047ng/mL). There was markedly elevated CRP (134.6mg/L) with no significant elevation for ASO titers and procalcitonin and rapid plasma regain was non-reactive. The stool and urine routine were normal, and stool, urine, and blood cultures showed no growth. Serology test showed negative for HIV I & II antibodies, HBsAg, and anti-HCV. Malarial Parasite antigen was also negative. RA factor, p-ANCA, and c-ANCA were negative, while ANA was found to be positive.

Ultrasound abdomen evaluation showed few enlarged mesenteric nodes with increased echogenicity of surrounding mesenteric fat strands and mild hepatosplenomegaly. Segmental areas of mild asymmetric bowel wall thickening and hyperenhancement of ileal loops with prominent mesenteric vasculature and mesenteric lymphadenopathy were noted on Contrast Enhanced Computerized Tomography (CECT).

Oesophago-Gastro-Duodenoscopy (OGD) revealed gastric ulcers and erosions, biopsies of these lesions showed chronic gastritis with parietal cell hyperplasia. Colonoscopy was suggestive of few erosions in the terminal ileum with multiple ulcers and erythema in the descending and sigmoid colon. Edema with neutrophilic vasculitis was evidenced by ileal biopsy, and colon biopsies were suggestive of features of focal active colitis with neutrophilic vasculitis. This clinical correlation led to diagnosis of vasculitis with gastrointestinal manifestation.

CASE 3: VASCULITIS PRESENTING WITH ACUTE ABDOMEN

A 35-year-old was male presented to emergency with acute onset pain in the right lower abdomen past 1 day, severe in intensity, radiating to back, and was associated with vomiting. USG was done which showed features suggestive of appendicitis. On examination, the patient was noted to have erythematous lesions on bilateral lower limbs, which was present for 1 week. He gave a history of a similar episode 4 years back. During his course at the hospital, he also developed blood-stained loose stools. Complete Blood count showed increased total counts (14,860 cells/cumm) with normal Hb, platelets, and differential counts.

CRP was elevated (75.59 mg/l), liver function test (LFT) showed elevated total bilirubin (1.5 mg/dL), with conjugated bilirubin of 0.43mg/dL, and an elevated ALP (172 u/L). Renal function test, serum electrolytes, amylase, and lipase were normal. Serology for HIV, HBsAg, HCV, Weil Felix, and Widal tests were negative. No growth was seen in stool culture.

USG of abdomen showed long segment circumferential wall thickening (Upto 6mm) in ileal loops in the right iliac fossa, likely of post-infective or inflammatory aetiology. Similar findings were noted on the CT abdomen, with no evidence of inflammation of the appendix. PET CT was performed, and no lesions were noted elsewhere in the body except for diffuse wall thickening of the distal ileum, as noted in other imaging studies (Figure 1). Upper GE endoscopy finding showed normal. Serum ANA, c-ANCA, and p-ANCA were negative. Weakly positive Mi-2 and borderline positive Scl-70 antibodies were seen on the ANA blot test. Skin and duodenal lesions were biopsied. Skin biopsy showed leukocytoclastic vasculitis and similar findings of leukocytoclastic vasculitis of small vessels of lamina priopria with focal cryptitis and increased mast cells were also seen on duodenal biopsy (Figure 2-4) . Based on the clinicopathological spectrum of he was diagnosed as Henous Schonlein Purpura (HSP).

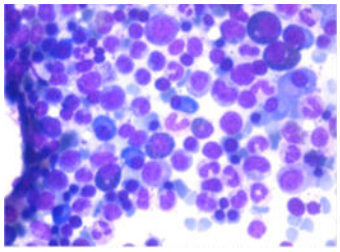

Figure 2: Bone marrow aspiration smear composed of moderately hyper cellular marrow with trilineage hemopoiesis and presence of both mature and immature plasma cells (Giemsa x100)

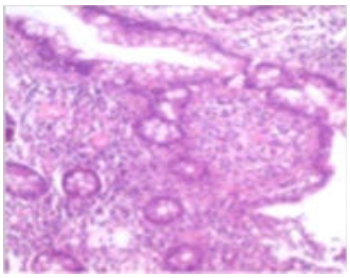

Figure 3b: Ileum blood vessels with neutrophilic infiltrate and fibrin

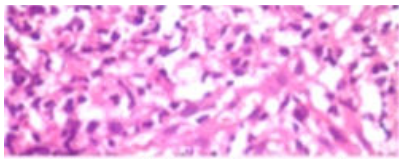

Figure 3c: Colon with neutrophilic vasculitis

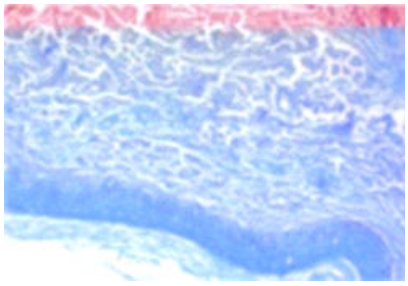

Figure 4a: Skin with dermal blood vessels with neutrophilic sculitis

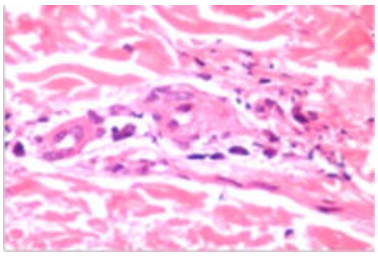

Figure 4b. Skin biopsy, dermal vessels with leukocytoclastic

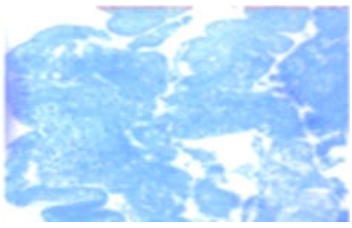

Figure 4c: Duodenal biopsy with neutrophilic vasculitis

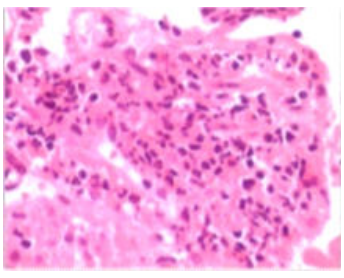

Figure 4d: Duodenal biopsy with neutrophilic vasculitis

DISCUSSION

Though vasculitis is rare, the potential for severe organ damage or death from these diseases, makes it imperative for the physician and pathologist to have a high degree of suspicion. It should be evaluated in patients who present with systemic or constitutional symptoms along with single and/or multiorgan dysfunction, and especially with some other key manifestations (skin, renal etc).

Malignancy can sometimes be a challenging diagnosis because of the possibility of multiple symptoms and clinical manifestations. Despite a well-recognized triad in multiple myeloma (anemia, hypercalcemia, and acute kidney injury), it is not always present, and there should always be a heightened clinical suspicion. Cutaneous manifestations in multiple myeloma are uncommon and have been classified as specific or nonspecific lesions. Cutaneous plasmacytoma is a specific but rare finding and easy to diagnose by histopathology. The disease develops from a precancerous condition called monoclonal gammopathy of undetermined significance (MGUS) [5] and has a variety of symptoms, including bone pain (60%), fatigue (30%), weight loss (25%), paresthesia (5%), fever (0.7%), hepatomegaly (4%), splenomegaly (1%), and lymphadenopathy (1%) [6-8]. Skin rash is a very rare manifestation of multiple myeloma [9]. Other skin findings are common dermatosis, such as leukocytoclastic vasculitis, urticaria, autoimmune bullous diseases, and pyoderma gangrenosum [10]. The first case depicts a rare manifestation of multiple myeloma. The patient presented with features suggestive of multiple myeloma. Plasmacytosis seen in bone marrow study led us to further strongly believe that this was a case of multiple myeloma. However, CRAB criteria suggested by the international myeloma working group were not met. The patient had fever associated with generalized myalgia, headache, and easy fatigability and complained of loss of appetite, weight loss, multiple joint pain, and bilateral shoulder pain. Müller et al. conducted a study over 25 years and reported that only 9 cases of fever were seen in 5,523 patients with multiple myeloma [11]. The patient's had high CRP, and ESR with and anemia were also present. The renal panel, lipid profile, stool routine, urine culture and blood culture were normal and ANA levels were negative. Accordingly, all the above findings confirmed multiple myeloma. Anemia is observed in 75% of patients, increased creatinine levels in 50%, and hypercalcemia in 25%. ESR is high due to increased immunoglobulins [12]. Since bone survey did not show any lytic lesion, decision was made to carry out a PET CT in an attempt to visualize any hypermetabolic lesions in the bones, but we were not expecting to see features of vasculitis and showed FDG uptake in the aorta, subclavian, and common iliac/femoral arteries which were suggestive of vasculitis. Upon the newfound evidence, a diagnosis of Giant Cell Arteritis was made as according to American College of Rheumatology Criteria [12]. Patient was later started on oral Prednisolone 60mg and Tocilizumab 162mg (s/c) once a week and later patient improved.

One important differential diagnosis for multiple myeloma is Waldenström macroglobulinemia. They are IgM monoclonal gammopathy, but there are some differences in clinical manifestations. Monoclonal immunoglobulin in the blood or urine and CRAB are seen in multiple myeloma, but in Waldenström macroglobulinemia, hepatomegaly and splenomegaly, anemia, lymphadenopathy, IgM component–related symptoms such as peripheral neuropathy, and constitutional manifestations are common. Clinical manifestation is a way to differentiate between these diseases [13-16].

GI vasculitis is a rare manifestation of SLE, and an accurate diagnosis and urgent treatment is needed to prevent the potential serious complications of necrotic bowel, perforation, and sepsis. The next case is of a 47-year-old male reported with GI vasculitis with features suggestive of Acute Diarrhea. Patient was initially given antibiotics and later it did not subside and later was investigated. Patient was found to have elevated inflammatory markers. As a result, patient was suspected to have Mesenteric Vein Thrombosis as stool routine and culture were found to be normal. CECT Abdomen and Pelivis was found to have Prominent Mesenteric Vasculature and Mesenteric Lymphadenopathy. The definitive diagnosis of GI vasculitis should be confirmed on histopathological examinations of mesenteric vessels in submucosal tissues, but some-times biopsies in endoscopic examinations might not yield a definitive diagnosis of GI vasculitis because the affected vessels are usually located in an inaccessible area, as seen in our case. Laparoscopy could be used in the definitive diagnosis of GI vasculitis. In our patient, the CT images showing bowel wall thickness, hyperenhancement of ileal loops with prominent mesenteric vasculature and mesenteric lymphadenopathy were noted. Biopsy of ileum was done which showed features of Vasculitis and later was started on Prednisolone 60mg and Cyclophosphamide 1gm every 2 weeks and later tapered and patient symptomatically improved. Therefore, the patient was diagnosed with vasculitis with GI manifestation according to clinical and imaging procedures.

The third case was diagnosed as Henoch Schonlein purpura (HSP). Henoch-Schönlein purpura is the most common systemic vasculitis in children with an annual incidence of six to 22 per 100,000 person-years in children and 3.4 to 14.3 per 100,000 person-years in adults [17]. The mean age of onset of HSP is six years old and it is twice as common in males than in females [18-20]. There are few reports presenting HSP in female adults as discussed and the atypical demographics of our patient could account for her delayed diagnosis. Examination plays a key role in diagnosing HSP and there are several common findings. Dermatological manifestations involve a symmetrical non-tender pruritic erythematous, macular, or urticarial rash, which develops into palpable purpura with blanching papules. The distribution of this rash varies depending on the age of the patient. Children under one-year-old develop a widespread rash involving the face, torso, and upper extremities, whilst in toddlers the rash typically involves the lower back and buttocks. In older children and adults, the rash is usually isolated to the lower limbs and buttocks [21]. Our patient presented with features of Acute Appendicitis and was initially conservatively managed. USG Abdomen showed wall thickenings in ileal loops and was thought. Inflammatory Bowel Disease. Later Biopsy was taken from duodenum and skin which showed features of small vessel vasculitis. Patient's initial cutaneous symptoms were consistent with the usual course of HSP in adults as described in the literature but progressed in an atypical manner affecting the upper limbs. Other examination features of HSP included gastrointestinal disturbance. In adult-onset HSP is more likely to present with arthralgia without arthritis [21]. The pattern of joint involvement is typically that of an oligoarthritic picture without redness, warmth, or erythema. In our case, the patient presented with acute-onset pain in right lower abdominal radiating to back. Despite this typical presentation, we suspect that the lack of cutaneous findings contributed to the missed diagnosis and exploration of a surgical abdomen. Renal involvement is

one of the main indicators of morbidity from HSP. Around 30% to 50% present with haematuria and or proteinuria within six weeks and the likelihood of developing renal pathology increases with the age of onset [22]. This is normally self-limiting, but around 7% develop a long-term nephritic or nephrotic condition and 1% develop end-stage renal failure. Severe renal involvement including progression to nephrotic syndrome and end-stage renal failure is more common in the adult population [23]. Our patient was found to have proteinuria and haematuria on urinalysis with a raised bilirubin and CRP, which is consistent with HSP nephritis. Although HSP is a clinical diagnosis, laboratory studies and imaging may help in more atypical cases. As well as routine laboratory studies, an extensive immune panel of blood may be required to support the diagnosis and rule out alternate pathophysiology, including ANA, ANCA, RF, and factors VIII and XIII levels. Imaging can also be considered, such as renal or skin biopsy, which may play a role when the diagnosis is uncertain or in monitoring for possible complications and system involvement. The management of HSP is largely supportive and involves a combination of analgesia, anti-emetics, hydration, and monitoring for complications. Treatments aim to provide acute symptom relief and prevent renal deterioration. Cutaneous involvement does not usually require management [24]. As HSP is characterized by IgA deposition and white cell infiltration within blood vessel walls, corticosteroids can play a role in inhibiting this inflammatory process [25]. One study found that 1 mg to 2 mg per kg of oral prednisolone for two weeks is effective for abdominal and joint symptoms. Other studies looking into the role of corticosteroids in HSP have found that although steroids do not prevent the onset of renal involvement, they are helpful for symptomatic relief (especially of abdominal and joint pains) [25,26]. Our patient was initially given NSAIDS for pain management and later after biopsy findings was started on Prednisolone 60mg and tapered. Patient improved symptomatically and was discharged.

Henoch-Schönlein purpura is usually self-limiting. Most patients completely recover with symptom resolution within eight to 10 weeks of onset and 5% develop chronic symptoms [27]. Complete clinical resolution is more likely in patients with mild renal involvement, no neurological complications, and a disease course of less than six weeks. Disease recurrence may occur in 30% to 50% of patients as late as seven years after the initial onset, and long-term follow-up studies have shown delayed-onset chronic kidney disease as a complication in cases where steroids were used in management [28].

CONCLUSIONS

These reports of cases have considerable results for guiding the clinicians, for optimal treatment regimens. Treatment of vasculitis depends on the etiology, the type of vasculitis, and extent and severity of disease. For exact categorization of vasculitis correlation with clinical features and immunological investigation is essential. This help to provide a window to the underlying systemic disorder and early management for the same.

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