ORIGINAL ARTICLE

Cutaneous Vasculitis: A Review of Aetiology and Clinical Manifestations in 85 Patients in Malaysia

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SUMMARY

Cutaneous vasculitis presents with a variety of clinical morphologies and causes significant morbidity. A total of 85 patients with cutaneous vasculitis at Hospital Kuala Lumpur were retrospectively reviewed. Palpable purpura was seen in 49.4% and frequently involved the lower limbs (50.6%). Identifiable causes include drugs (28.2%), infections (20.0%) and connective tissue disorders (16.5%). Non steroidal anti-inflammatory were the commonest group of drugs responsible for 25% of cases while β-haemolytic streptococci was the leading infectious cause (64.7%).

KEY WORDS:
Cutaneous vasculitis, Palpable purpura

INTRODUCTION

Vasculitis is a condition characterized by inflammatory destruction leading to haemorrhage and ischaemia of blood vessels. The pathogenesis is immune mediated resulting in the deposition of antigen-antibody complexes in vessel walls leading to fibrinoid necrosis and vessel wall injury. It may be confined to the skin (cutaneous vasculitis) or involve other organ systems with multiple extracutaneous end organ damage resulting in significant morbidity[1,2]. Characteristic clinical presentation includes palpable purpura, urticaria, infitrated erythema, ulcer, infarct, livedo reticularis, nodules and gangrene.

To date there is no published data regarding cutaneous vasculitis and its possible underlying aetiologies in Malaysia. A retrospective study was conducted to determine the demography, clinical features and the possible underlying aetiologies of cutaneous vasculitis at the Department of Dermatology, Hospital Kuala Lumpur.

MATERIALS AND METHODS

A retrospective review of patients who were clinically diagnosed with cutaneous vasculitis at the Dermatology Department of Hospital Kuala Lumpur from January 2002 to December 2006 were included. Cases registered under vasculitis, connective tissue diseases, polyarteritis nodosa, Henoch-Schonlein purpura, Behcet's disease, and dematomyositis were selected using the clinic computer database and the case notes were screened manually. Case notes with clinical diagnosis of cutaneous vasculitis were selected. Data extracted from case notes include patient information, clinical presentation of vasculitis, history of drug intake and summary of the investigation results.

RESULTS

A total of 85 patients were analysed. The number of females to males affected with cutaneous vasculitis was almost equal (1.4:1). This is similar to the ratio of females to males who attended this clinic from year 2002-2006 (1.2:1). The distribution among the different races was Malays 60%, Chinese 20%, Indians 12.9% and other races 7.1%. This pattern closely resembled the racial distribution of patients who attended the dermatology clinic during the same period (Malays 59%, Chinese 20%, Indians 19% and Others 2%). The patients' age at presentation ranged from 13 to 93 years with a mean of 36.5 years. Patients in the age group 20 to 39 years were most frequently affected (47.1%).

About half of the patients presented with palpable purpura (49.4%) followed by non-palpable purpura (12.9%), urticaria (11.8%) and ulcers (9.4%). The lower limbs only were most commonly involved (50.6%), followed by upper and lower limbs (18.8%) and generalized distribution (17.6%).

Haematological investigations showed that the erythrocyte sedimentation rate (ESR) was raised in 92.3% of the patients. Other investigations that were carried out and their results are summarized as in Table I. Most of the blood investigation results were within normal range.

Skin biopsy was performed for 57.6% patients and all were consistent with histopathology of cutaneous vasculitis. The commonest histopathological manifestation was leucocytoclastic vasculitis (67.3%) followed by lymphocytic vasulitis (14.3%). Direct immunofluroscence was performed in 46.9% samples, out of which only 13.0% (three patients) were positive. Two had IgG and C3 while one had IgM and C3 deposited around the vessel wall.

A possible aetiology for vasculitis was found in more than half (67.1%) of the patients. The most common underlying etiology was drugs (28.2%) followed by infections (20.2%) and connective tissue disorders (16.5%) as displayed in Table II. Among the drugs, non steroidal anti-inflammatory drugs were most commonly (25%) implicated (Table III).

Among the infective causes, β-haemolytic streptococci was the leading cause (64.7%) followed by Hepatitis B (29.4%) and

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Table I: Haematological investigation results

Investigation	Number of patients tested	Percentage with abnormal results	Percentage with normal results
Anti Nuclear Antibody (ANA)	61	9 (14.8%)	52 (85.2%)
Erythrocyte Sedimentation Rate (ESR)	52	48 (92.3%)	4 (7.7%)
Complement Level (C3 & C4)	34	14 (41.2%)	20 (58.8%)
Hepatitis B surface antigen (HBs Ag)	32	5 (15.6%)	27 (84.4%)
Anti Streptolysin O Titer (ASOT)	28	11(39.2%)	17 (60.7%)
Antibodies to Hepatitis C Virus (Anti HCV)	26	1 (3.8%)	25 (84.4%)
Renal Function	25	2 (8.0%)	23 (92.3%)
Antineutrophil cytoplasmicantibodies (p & c ANCA)	23	4(17.4%)	19 (82.6%)
Protein electrophoresis	13	1 (7.7%)	12 (92.3%)
Cryoglobulin	11	0 (0%)	11 (100%)
Throat swab	10	0 (0%)	10 (100%)
Double Stranded DNA (dsDNA)	9	2 (22.2)	7(77.8%)
Extractable Nuclear Antibodies (ENA)	7	0 (0%)	7(100%)
Protein C & S	2	1 (50%)	1 (50%)

Table II: Etiology of Cutaneous Vasculitis

Causes	Number of cases (Percentage)
Idiopathic	28 (32.9%)
Drug	24 (28.2%)
Infection	17 (20.0%)
Connective tissue disease	14 (16.5%)
Malignancy	2 (2.4%)
Total	**85 (100.0%)**

Table III: Drug Related Cause

Drugs	Number of cases (Percentage)
Analgesics	
NSAIDs	6 (25.0%)
Antibiotics/ Antiviral	
Cephalosporin	4 (16.5%)
Penicillin	1 (4.2%)
Vancomycin	1 (4.2%)
Ofloxacin	1 (4.2%)
Unasyn	1 (4.2%)
Unknown	2 (8.1%)
Antihypertensive	
Amiodarone	1 (4.2%)
Perindopril	1 (4.2%)
Others	
Persantin	1 (4.2%)
Ranitidine	1 (4.2%)
Sildenafil	1 (4.2%)
Traditional Medication	1 (4.2%)
Combination of antibiotic and antihypertensive	1 (4.2%)
Lamivudine	1 (4.2%)
Total	**24 (100%)**

Hepatitis C (5.8%). Systemic lupus erythematosus (SLE) contributed to 71.4% of connective tissue diseases as the etiology for cutaneous vasculitis followed by mixed connective tissue disease (21.4%) and Sjogrens syndrome (7.2%).

DISCUSSION

Cutaneous vasculitis affected all age groups, but more commonly between the 20 to 40 years. It occurred among males and females equally, without any racial preponderance. The lower extremities were preferentially affected. This could be due to the fact that these are dependent areas with sluggish blood flow, hence facilitating deposition of immune complexes. A more disseminated pattern would indicate a possible underlying systemic disease or a more severe disease process[3]. The commonest presentation in this study was palpable pupura, which is similar to other studies[4,5]. A more chronic or persistent course of the disease can be anticipated if ulcers were the initial presenting features compared to palpable purpura[3].

The commonest aetiology was drugs, followed by infections and connective tissue diseases. Some studies have shown that vasculitis secondary to drugs or infection is usually a single episode with an onset of between 7 to 10 days after exposure and has good recovery rates with 60% of them resolving spontaneously within 6 months[4]. A protracted course of vasculitis, lasting six months to years with frequent relapses was found to be associated with connective tissue disease[3,5,6]. Hence cutaneous vasculitis with chronic relapses should be screened for connective tissue diseases as a possible underlying cause.

Two patients of the elderly age group (2.4%) in this study had an associated malignancy. One had chronic myeloid leukemia and the other had Non-Hodgkin's lymphoma. One study has shown that malignancy although an uncommon cause is responsible for 2.3% of vasulitis[7]. Malignancies that are most commonly responsible for clinical manifestations of cutaneous vasculitis representing a paraneoplastic phenomenon are haematological malignancies (90%)[7]. The majority of individuals with leukocytoclastic vasculitis secondary to haematological disorders suffer from lymphoid neoplasms, most commonly lymphoproliferative (almost 20%) or myelodysplastic syndrome (3-5%)[8]. This type of vasculitis is usually chronic, unremitting and fails to respond to treatment. Patients of older age group with cutaneous vasculitis and associated fever, weight loss and night sweats should be screened for an underlying malignancy[3].

The commonest histopatological finding in this study was leucocytoclastic vasculitis with extravasations of red blood cells and inflammatory infiltration consisting predominantly of neutrophills (67.3%). Vessel wall injury occurring in

vasculitis is mostly immune mediated with a morphological pattern identical to fibrinoid necrosis[7]. This common end point is due to activation of neutrophils and neutrophil diapedesis which may be the common factor in the pathogenesis of neutrophil associated small vessel vasculitis.

The results of the direct immunofluorescent test performed on biopsy specimens in this study were mostly (87%) negative. Direct immunofluorescent is not a diagnostic test and is found to be negative in about 20 - 40% cases[9].

ESR was noted to be raised in most of the patients while other investigations, such as throat swab, cryoglobulin and Extractable Nuclear Antigen (ENA) were within normal limits. Low levels of complement (C3 and C4) were detected in 14 patients. Some studies have shown that low complement levels have been associated with a more aggressive pattern of the disease and a less favorable outcome[3]. A raised Antistreptolysin O titer (ASOT) in patients with cutaneous vasculitis is suggestive of a probable recent streptococcal infection and appropriate antibiotics should be prescribed. One has to remember that these medications by itself may further aggravate the underlying vasculitis.

A number of screening investigations are performed to evaluate the possible underlying etiology of cutaneous vasculitis. Blood investigations have a limited role for identifying underlying cause and should be only performed for patients with symptoms or associated features e.g. connective tissue disease or in protracted case where the cause is unclear. Most investigations performed in this study showed normal values. This raises the question of cost effectiveness and usefulness of these investigations as a screening tool to identify the underlying aetiology for cutaneous vasculitis.

Limitations faced in this study would include problems associated with a retrospective study. A prospective review which evaluates outcome of treatment would provide useful information regarding appropriate choice of therapy. Selective bias in this study cannot be ruled out as only the cases which were registered in the computer data base were analyzed. Cases diagnosed prior to starting the registry may have been unintentionally excluded.

CONCLUSION

This study shows that the commonest presentation of cutaneous vasculitis was palpable pupura which mainly affected the lower limbs. The most common causes of cutaneous vasculitis were drugs followed by infection and connective tissue disease. Non-steroidal anti-inflammatory drugs (NSAIDs), were the commonest drug responsible for vasculitis. This highlights the importance of a detailed drug history in patients presenting with cutaneous vasculitis. It may cause future concern with the increasing consumption of non-prescribed over the counter drugs, combined with under-reporting of its usage[4,10]. Screening for infections especially Hepatitis B and C and connective tissue diseases should be considered in geographical areas where these diseases are found in higher frequencies.

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