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Spectrum of secondary vasculitis seen at tertiary care hospital

KEYWORDS: Secondary vasculitis, infection, cutaneous vasculitis, systemic vasculitis, tuberculosis, malignancy, drug-induced vasculitis.

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ABSTRACT

Objective: *To evaluate the patterns and clinical characteristics of secondary vasculitis.*

Methods: *An observational cross-sectional study was conducted at Command Hospital, Chandigarh and at INHS ASVINI, Mumbai Patients who were suspected to have vasculitis were enrolled in to study from September 2013 to August 2014.*

Results: *Thirty-seven cases of secondary vasculitis were studied. The average age of patients was 45 years and majority of the study population was women. Causes of secondary vasculitis in our study were: (a) Infections (29.7% [11/37]; hepatitis C infection with cryoglobulinemia [n=1], human immunodeficiency virus [n=1], Mycobacterium tuberculosis infection [n=5], fungal infection [n=1] and bacterial infections [n=3]) (b) rheumatoid arthritis (0.8% [03/37]), (c) malignancy (13.5% [05/37]; colon carcinoma [n=1], cervical carcinoma [n=2], and non-Hodgkin's lymphoma [n=3]), (d) lupus in 32.4 % [12/ 37] and (e) drugs (10.8% [04/37]). Skin was the predominant organ affected by vasculitis (64.9%). Musculoskeletal system (45.9%), eyes (10.8%), neurological (2.8%) and kidneys (32.4%) were other organs that were frequently involved in vasculitis in our patients.*

Conclusion: *This study demonstrated that secondary vasculitis is a common finding and most often associated with infection. Skin is the commonest organ to be involved in secondary vasculitis. Histological or radiological proof of vasculitis is warranted, and where possible, the specific type of vasculitis should be identified.*

Introduction

Vasculitis, characterized by inflammation and necrosis of blood vessels, presents with highly diverse group of clinicopathological entities. Vasculitis occurring in the absence of any precipitating factors or associated diseases is primary vasculitis. Secondary vasculitis occurs secondary to any established diseases, infection, malignancy or drugs. Vasculitis can affect any type of blood vessel supplying to any organs and therefore the clinical manifestation and prognosis varies. The signs and symptoms of vasculitis depend on the site, type and size of vessels involved. Vasculitis may occur as either a benign and dormant disease restricted to a single organ/vessel or fulminant life-threatening systemic vasculitis.[1–3] Patients usually present with B-symptoms (malaise, weight loss, fever and night sweats), which reflect constitutional symptoms.[2] The clinical symptoms of vasculitis usually mimic many other medical conditions. Overall, diagnosing vasculitis is challenging owing to its variable clinical manifestation. It is very rare to diagnose vasculitis at the outset. Vasculitis should be suspected in those patients where systemic disease involving multiorgan is not associated with infection or malignancy. Therefore, physicians have to be rational in their approach while evaluating patients with suspected vasculitis.

Objectives

In the absence of a definite diagnostic work-up and challenging clinical presentation of vasculitis, we undertook a study to evaluate the patterns and clinical characteristics of secondary vasculitis.

Materials and methods

We conducted an observational prospective study at Command Hospital, Chandigarh and at INHS ASVINI, Mumbai from September 2013 to August 2014. We included all patients diagnosed with secondary vasculitis during study period in this study. All those patients who had multisystem involvement were included. Also those having single organ involvement and having histopathological diagnosis consistent with vasculitis were also included. All those patients who were not fulfilling classification criteria for primary vasculitis were included in this study. These patients were subjected to Rheumatoid factor, anti CCP antibody assays, Cytoplasmic antineutrophilic cytoplasmic antibodies, and Anti-nuclear antibody testing.. They were also studied for presence of disseminated tuberculosis, evidence of infective endocarditis, malignancies, or infection with hepatitis viruses and human immunodeficiency virus (HIV). We excluded patients with primary vasculitis, or patients not willing to participate in the study. The principal investigators assessed all admission and discharge papers, case sheets, laboratory investigation report and referral forms.

All those patients who were not fulfilling classification criterion for primary vasculitis were included in this study.

Inclusion criteria

- Multisystem involvement
- Single organ involvement with proven or suggestive of vasculitis

Exclusion criteria

All those patients who were fulfilling classification criterion for primary vasculitis were excluded in this study.

Results

Total study population was 48 and 37 patients with secondary vasculitis were included and 11 excluded. The average age of patients was 45 years and the study population comprised predominantly women (n=34). Causes of secondary vasculitis in our study were infections, Rheumatoid arthritis, malignancy and drugs (Figure 1). Among those with infection, one patient each had hepatitis C infection with cryoglobulinemia, HIV, and fungal infection. Five patients had tuberculosis and three had bacterial infections. Malignancy included colon cancer (n=1), cervical cancer (n=1), and non-Hodgkin's lymphoma (n=3). Skin and musculoskeletal system was the predominant organ affected by vasculitis (Figure 2).

Table 1. Cause of secondary vasculitis

Disease	Number of patients
Infections	11
Bacterial	3

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Human immunodeficiency virus	3
hepatitis C infection	1
Tuberculosis	5
Fungal	1
Rheumatic arthritis	3
Malignancy	5
Solid organs	2
Non-Hodgkin lymphoma	3
Drugs	4
Septran	2
Allopurinol	2
Lupus Erythematosus	12
Sjogren's syndrome	2
Sarcoidosis	1
n	37

Table 2. Organs involved in secondary vasculitis

Organ involved	Number of patients
Skin	24
Musculoskeletal system	17
Kidney	12
Respiratory system	8
Gastrointestional	4
Central nervous system	1
Eye	4

Discussion

Secondary vasculitis includes a variety of syndromes. Rheumatoid vasculitis is one the most commonly recognised form of secondary vasculitis. Drug therapy also causes some type of vasculitis.[4] The complex and diverse pathophysiology of secondary vasculitis renders itself as a diagnostic challenge to physicians.

Overall, four major reasons for secondary vasculitis was identified in our study population and those included infections, rheumatoid arthritis, malignancy and drug therapy. The distribution of vasculitis was almost the same among the causes and in one-fifth of the cases, the etiology of secondary vasculitis was unknown. In nearly 40% of them, skin was involved. Musculoskeletal system was next commonly affected system followed by eyes, kidney and nerves.

Infections act as a trigger or are a reason for some types of vasculitis.[4] Infections may be the reason for primary or secondary vasculitis.[5,6] Different infectious agents or infections damage the vascular wall either directly by destroying the blood vessel or indirectly by stimulating an immune response against vascular wall. At times, a mix of both direct and indirect mechanisms can trigger secondary vasculitis. Microbial agents, such as *Mycobacterium tuberculi*, *Mycobacterium leprae*, hepatits B virus, and HIV trigger vasculitis in the indirect way. On the contrary, microbial agents such as *Staphylococcus* spp, *Streptococcus* spp, *Salmonella* spp, *Treponema* spp, *Rickettsia* spp, cytomegalovirus, herpes simplex virus 1 and 2 cause vasculitis by a direct action on the vascular wall.[7]

Several case studies haves shown the occurrence of vasculitis in HIV patients. Immunological factors or direct vascular injury can cause vasculitis in patients with HIV.[8] Almost all types of vasculitis reportedly affect about 1% of the HIV population.[9] A case study described cerebral vasculitis secondary to Epstein-Barr virus in newly diagnosed HIV patient.[10] Bilateral retinal vasculitis and recurrent vitreous hemorrhage was reported in a patient with HIV and syphilis.[11] A HIV positive child reportedly developed Dejerine-Roussy syndrome due to cytomegalovirus vasculitis.[12] Polyarteritis nodosa (PAN)-like vasculitis is another rare form that is associated with HIV infection.[13] HIV-associated carotid vasculitis could cause cerebral infarction.[14]

Ocular complications are seen in 70–80% of positive untreated HIV patients. Peripheral retinal vasculitis was found in a patient with untreated HIV infection.[15] There are concerns that rising prevalence of HIV and hepatitis C virus coinfection could perhaps increase the risk of vasculitis, as well and pose a bigger diagnostic and treatment challenge.[16]

Hepatitis C virus-related systemic vasculitis may occur in the absence or presence of detectable mixed cryoglobulinemia. Hepatic and mesenteric vasculitis was reported in a patient with chronic hepatitis C virus infection with mixed cryoglobulinemia.[17] A patient with chronic hepatitis-C virus infection presenting with livedo reticularis, purpura, and leg ulcers was diagnosed with necrotizing vasculitis.[18] Necrotizing vasculitis was histologically confirmed in a patient with type II cryoglobulinemia and hepatitis C virus infection.[19] Cutaneous leukocytoclastic vasculitis has been a common finding in patients with hepatitis C virus infection with cryoglobulinemia.[20–22] In our study, one patient presenting with hepatitis C infection with cryoglobulinemia had developed secondary vasculitis.

There are no reports about fungal infection as a cause of secondary vasculitis but in our study, one patient with fungal infection had developed secondary vasculitis.

Cutaneous leukocytoclastic vasculitis is a rarely reported to be associated with tuberculosis or anti-tubercular drugs.[23,24] In a study, *Mycobacterium tuberculi* infection and active tuberculosis were found to be associated with the development of erythema nodosum and nodular vasculitis.[25] In a young and immunocompetent patient, cutaneous leukocytoclastic vasculitis was indicative of an underlying pulmonary tuberculosis.[26] A case study reported perforation of the nasal septum as a vasculitis complication because of tuberculosis.[27]

Cutaneous vasculitis is an overwhelming extra-articular manifestation of rheumatoid arthritis and the clinical manifestation of digital vasculitis are necrosis, ischemia, infarction, and eventually gangrene.[28] Vasculitis is a rare complication of immune-adsorption treatment with staphylococcal Protein A (Prosorba column) with a prevalence of 7 per 400 in patients with rheumatoid arthritis.[29] Acute cholecystitis resulting from vasculitis of the gallbladder is an extremely rare manifestation of rheumatoid vasculitis.[30]

A review of literature shows that patients with certain types of vasculitis are likely to be at increased risk of cancer and on the contrary, vasculitis is also a likely manifestation of malignancy.[31] Depending on the nature of the malignancy and the subtype of vasculitis, the clinical manifestation of vasculitis during malignancy is heterogeneous.[32] Vasculopathic syndromes in malignancies are a rare association. Seldom, vasculitis is a complication of cancer treatment (chemotherapy, radiation therapy, and bone marrow transplantation). Usually, vasculitis as a cutaneous complication (skin lesion) of cancer is limited to hematologic malignancies and is very less frequently associated with solid tumors.[33]

Certain drugs have the potential to cause vasculitis. Skin is the primary target of drug-induced vasculitis and sometimes kidneys and lungs are affected. Propylthiouracil, hydralazine, colony-stimulating factors, allopurinol, cefaclor, minocycline, D-penicillamine, phenytoin, isotretinoin, and methotrexate are the drugs that are implicated in drug-induced vasculitis.[34] Minocycline and anti-tumour necrosis factor (adalimumab etanercept, or infliximab) can induce cutaneous vasculitis.[35] Discontinuation of drug rather than initiating immunosuppressive and anti-inflammatory drugs may help in regressing vasculitis.[36]

A review of literature shows that secondary vasculitis is a heterogeneous manifestation of various diseases or treatment for diseases. In our study also, we found the cause of vasculitis to be diverse. Infections do play a major role in the development

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of vasculitis. Autoimmune disorders such as rheumatic arthritis also cause vasculitis. Malignancy is usually associated with cutaneous vasculitis.

Conclusion

Concurrent to literature reviews, in our study also, we found secondary vasculitis to be a heterogeneous with diverse group of clinicopathological entities. Secondary vasculitis is a common manifestation of infection in our study. Skin is the commonest organ to be involved in secondary vasculitis. The characteristic diverse clinical manifestation of vasculitis renders it a more difficult condition to diagnose and treat. In this context, a complete physical examination along with standard laboratory and radiologic examinations is necessary to confirm the diagnosis of vasculitis. In certain cases, magnetic resolution imaging, computed tomography or X-rays may be needed.

Our study further highlights that

- Clinical manifestations can be systemic and/or organ-specific, depending on how vessels are affected.
- Vasculitis tends to affect small-, medium-, or large-sized vessels, each with certain patterns of organ involvement.
- Blood tests, imaging studies, and tissue biopsy are warranted to determine the cause of vasculitis (including disorders such as infections and cancer) and extent of organ involvement.

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