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RESEARCH ARTICLE

Hepatitis C Virus Infection as a provocative agent for cutaneous vasculitis

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Abstract

Background: Several patients with chronic hepatitis C infection and cutaneous vasculitis have
been described.

Objective: This work was done to detect if there is an association between cutaneous vasculitis and HCV infection and to detect how far HCV is an elective agent for cutaneous vasculitis.

Methods: The study included 20 patients with cutaneous vasculitis (group I) and 30 patients with HCV infection (group II). Histopathological examination was done for biopsies taken from cutaneous vasculitic lesions and were stained with haematoxylin & eosin (H&E) and Periodic acid-Schiff (PAS) stain. Liver function tests of the patients were assessed Also, detection of HCV antibodies was done by using electrochemiluminescence immunoassay.

Results: Of the 20 patients with cutaneous vasculitis included in this study, Anti-HCV antibodies were detected in 12 patients (60%). On the other hand, of the 30 patients with hepatitis C infection included in group 2 of this study, 2 patients with cutaneous vasculitis were identified (6.6 %). However, there was no significant difference as regard Liver function tests and histopathology between HCV positive and negative cases.

Conclusion: This study showed that the presence of cutaneous vasculitis should suggest that a hepatitis C virus may be a possible etiological or provocative agent..

INTRODUCTION

epatitis C virus (HCV) is an RNA virus with 6 major genotypes. HCV causes both acute and chronic hepatitis, cirrhosis, and liver cancer.[1] Besides its hepatic manifestations, HCV infection is commonly associated with extrahepatic disease including hematologic, dermatologic, renal, autoimmune, neurologic, endocrinal, cardiac, and pulmonary disorders.[2,3]

Hepatitis C Virus is associated with a wide series of extrahepatic manifestations. Mixed cryoglobulinaemia represent the most closely related extrahepatic manifestations of Hepatitis C Virus.[4] Other Hepatitis C Virus-associated disorders include leuko-cytoclastic vasculitis, porphyria cutanea tarda, sicca syndrome and lichen planus.[5]

HCV infection is a common cause of cutaneous vasculitis. Cutaneous Vasculitis is an inflammatory process affecting the vessel wall and leading to its compromise or destruction and subsequent hemorrhagic and ischemic events. The inflammation can affect any of the vessels in the skin including capillaries, venules, arterioles and lymphatics. Cutaneous vasculitis can be due to any of several different causes and can have a wide variety of clinical

presentations.[6] Underlying autoimmune diseases, malignancy, drugs and systemic vasculitis are often found to be aetiological factors. Infections also play a major role including streptococcus, staphylococcus, mycobacterium and hepatitis B or C viruses.[7] In most cases an underlying cause is not found and the disease is self-limiting. Patients may present with skin symptoms such as lesions, including palpable purpura, urticaria, ulcers, livedo reticularis, and nodules. If cutaneous vasculitis occurs as part of a systemic vasculitis, symptoms may also include fever, arthralgias, other organ involvement, or a combination.[8] The diagnosis of vasculitis is confirmed unequivocally by the presence of an inflammatory infiltrate around and within the walls of vasculature with fibrin deposition. These areas of fibrinoid necrosis are accompanied by swelling and necrosis of endothelial cells, as well as secondary changes such as erythrocyte extravasation and necrosis leading to purpura and infarction, respectively.[9] Apoptotic cells are seen frequently as well as overlying ulceration. Determination of vessel size, type of cellular infiltrate, depth, and degree of involvement on H&E stains helps in classification and generation of differential diagnoses. The pathogenic features of vasculitis in the skin are related to vessel wall injury, which can be toxin mediated, immune mediated, or from direct infection, and all three mechanisms can result in the histologic pattern of fibrinoid necrosis mentioned above.[10]

This work was done to detect if there is an association between cutaneous vasculitis and HCV infection and to detect the vasculitic changes on top of HCV infection.

METHODS

Patients

This study was conducted on two groups, Group I included 20 patients with different types of vasculitic lesions, 8 males and 12 females, their age ranged between 22-65 years with a mean age of 49.7 years.

Group II included 30 patients with HCV infection, 21 males and 9 female, their age ranged between 40-62 years with a mean age of 48.75 years.

All patients were subjected to the following: full history taking and dermatological examination. Pathological study of the cutaneous lesions were done by examination of their skin biopsies. Skin biopsies were stained with haematoxylin and eosin (H&E) stain and Periodic acid-Schiff (PAS). Liver function tests of the patients were assessed using screening tests including serum ALT, AST, total and direct bilirubins, total protein and albumin. Also, detection of HCV antibodies was done by using electrochemiluminescence immuno-assay (ECLIA).

Skin biopsy taking and Pathological study of the cutaneous lesions: Skin biopsy was taken under strict aseptic conditions, using 5 mm disposable skin punch biopsies. Local anaesthetic (1% xylocaine) was injected intradermal into the area to be excised. Each specimen was fixed in 10% neutral formalin solution and embedded in paraffin blocks and serial sections of 4 micron thickness were obtained from each block and stained with H&E stain and PAS stain then refered to the histo-patholgical department to be examined pathologically.
Detection of HCV antibodies: The Detection of HCV antibodies was done by the electro-chemiluminescence immunoassay (ECLIA) using cobas e 411 analyzer.

Study methods

Statistical methods: The Statistical analysis of the data in the present study was done using the (SPSS) version 15 as the data are coded, entered and checked to statistical package for social science (SPSS) version 15. Mean± SD was used. Student's test was used For comparison between two grouped means. Chi – square (X^2) was Used to find the association between raw variables and column variables.

RESULTS

P less than 0.05 was considered to be significant and less than 0.01 was considered to be highly significant.
This study was conducted on 50 patients. They were classified into 2 groups, **Group I :** Included 20 patients with cutaneous vasculitis, 8 males (40%) and 12 females (60%). Their age ranged between 22-65 years with a mean age of 49.7± 6.8 years. **Group II :** Included 30 patients with HCV infection, 21 males (70%) and 9 females (30%). Their age ranged between 40-62 years with a mean age of 48.75± 12.5 years.

In group I among the 20 patients with cutaneous vasculitis, HCV-Ab was positive in 12 patients. While in group II, only 2 patients from the HCV patients were found to have vasculitic lesions.

HCV-Ab was positive in 12 patients, 4 males(33.3%) and 8 females (66.7%), their age ranged between 24-64 years with a mean age 49.1± 12.0 years. HCV-Ab was negative in 8 patients, 4 males (50 %) and 4 females (50 %), their age ranged between 22- 65 years with a mean age of 48.3±13.7 years.

According to clinical examination, 18 patients of Group I had palpable purpura (90%) and two out of the twenty patients hemorrhagic crust and erythematous papules were noted.

As regard the duration of cutaneous vasculitic lesions, there was no significant difference between HCV positive and HCV negative patients with cutaneous vasculitis in group I. The mean ±SD of the duration of cutaneous vasculitic (15.7± 24.6 versus 10.5 ± 16).

In this study, in 50% of patients of goup I, cutaneous vasculitis was associated with some clinical data. They were in the form of generalized lymphadenopathy (5%), lymphoma (10%), systemic lupus erythrmatoses (10%), leukemia (5%), rheumatoid arthritis (5%), psoriasis (5%), deep venous thrombois (5%) and autoimmune disease (5%). On the other hand, no association by other clinical data was detected in patients of group II.

Regarding the types of vasculitis , the histopathological examination revealed 17:20 (85%) had leukocytoclastic vasculitis, 3/20(15%) patients had lymphocytic vasculitis.

There was no significant difference between cutaneous vasculitis lesions in HCV +ve and HCV -ve cases detected as regard Major criteria (Polymorphonuclear leukocytes (PNL) infiltration + Nuclear dust, lympocytic infiltration and fibrinoid necrosis) and minor criteria (endothelial swelling, epidermal necrosis, thrombosis, perivascular haemorrage, interstitial infiltration, perivascular fibroplasias and sweet gland/duct necrosis) .

Among the two major criteria, infiltration of the wall by PNLs was the predominant and the most common minor criteria was perivascular hge(RBCs) followed by endothelial swelling then mixed interstial infiltrate. While the non presented criteria in our cases was perivascular fibroplasia & calcinosis.

The biopsy of cutaneous vasculitic lesions were stained also with Periodic acid-Schiff (PAS) stain. It is known that deposition of amorphous PAS +ve substance can represent cryoglobinemia related to HCV.[11] In this study 2 cases of cutaneous vasculitis with HCV postive were positive for deposition of amorphous PAS substance, which suggest the possibility of being cryoglobulinemic vasculitis .

As regard the liver function tests, there were no significant difference between HCV positive and HCV negative patients with cutaneous vasculitis in group I. The mean±SD of AST (36.8±21.86 versus 34.8± 21.2), ALT (41.2±34.05 versus 42.1±22.8), albumin (3.27±0.37 versus 3.63±0.5), bilirubin (1.1±1.3 versus 0.73±0.93).

On the other hand on comparing the liver function tests between group I and group II , group II showed higher means than group I and the difference were highly significant ($P<0.01$).

DISCUSSION

The Prevalence of cutaneous manifestations with HCV infection universally is different. It may be related to the endemic presence of HCV infection. Therefore, the prevalence varies from country to country. In turn, particular HCV genotypes and unknown environmental and/or genetic factors may contribute to this difference. Of the 20 patients with cutaneous vasculitis included in this study, Anti-HCV antibodies were detected in 12 patients (60%). Several authors reported about the prevelance of HCV in patients with cutaneous vasculitis. The association of cutaneous vasculitis with hepatitis was first reported by Popp et al. (1981)[12] in 5 patients, 1 with hepatitis B and 4 with non-A, non-B hepatitis. Theilmann et al.(1991)[13] described 56 patients with systemic vasculitis, 2 (3.5%) of them being positive for HCV. Gungor et al. (1999)[14] found anti-HCV antibodies in 2/25 patients with leucocytoclastic vasculitis (8%) and none of the control group.

In Egypt, a previous study was done by Ibrahim et al. (1999)[15] in which the prevalence of HCV infection in patients with cutaneous vasculitis was found to be (36.8%).

In our study this high association (60%) between cutaneous vasculitis and HCV may be related to the high endemicity of HCV in Egypt , also to the HCV genotype present (mainly genotype 4). Moreover, to the onset of skin lesions that proposed to be usually more than 10 years after HCV infection [16], which is concident with the chronicity of HCV infection.

On the other hand, of the 30 patients with hepatitis C infection included in group 2 of this study, 2 patients with cutaneous vasculitis were identified (6.6 %).

Cutaneous vasculitis was identified in 10 of 408 HCV infected patients in one study (2.5%)[17] and in 12 of 611 in another study (2%) [16] In 2005 Dervis and Serez [18] found 3 of 70 patients with chronic HCV infection (4.28%) had leukocytoclastic vasculitis

In Egypt,2009, Raslan et al.[19] found 4 of 155 patients with chronic HCV infection (2.6 %) had leukocytoclastic vasculitis.

It should be pointed out that in this study, cutaneous vasculitis associated with HCV infection occurred chiefly in the fifth to sixth decades of life, and male to female ratio was 4:8. This result was similar to that obtained by Buezo et al. (1996)[20] as they reported that females were predominantly affected and male to female ratio was 1:7.

In this study, palpable purpura is the most common manifestation of cutaneous vasculitis founded in this study (90%). In 2009 Leelavathi et al[21]stated that palpable purpura was seen in (49.4%) of a studied patients group with cutaneous vasculitis in Malaisia. Also in Spain**,** 2004 López de Maturana et al [22] reported that palpable purpura is the most common manifestation (62%) of cutaneous small vessel vasculitis, In Syria, 1996 Daoud et al.,[16] found that Palpable purpura was the most common presentation (100%) of cutaneous vasculitis associated with HCV infection.

Cutaneous vasculitis is associated with idiopathic disorders or chronic disorders including rheumatoid arthritis, ulcerative colitis, lymphoproliferative disorders, cryoglobulinemia, cystic fibrosis, systemic lupus erythematosus, and other connective tissue diseases. Precipitating factors of cutaneous vasculitis include infections (e.g., hepatitis B virus, and HCV) and medications (e.g., penicillin, sulfonamide, thiazides, and certain nonsteroidal anti-inflammatory drugs)[23]

In this study cutaneous vasculitis was associated with some clinical data (50 %). They are in the form of generalized lymphadenopathy (5%), lymphoma (10%), systemic lupus erythrmatoses (10%), leukemia (5%), rheumatoid arthritis (5%), psoriasis (5%), deep venous thrombois (5%) and autoimmune disease (5%).

As regard cases of cutaneous vasculitis associated with HCV +ve infection, the associated clinical data is (30%).

It is well known that underlying autoimmune diseases, malignancy, drugs , infections and systemic vasculitis may be found to be an aetiological factors.[7] But they have prevalence rates of not more than 13%[14]

On the other hand, HCV infection induces autoimmune process, which may be the cause of other clinically associated data as psoriasis [19], lymphoma [4,] Cryoglobulin-aemia and rheumatoid disorders. [2]

Skin biopsies were taken from all vasculitic patients and under went histopathological examination, which reveals no significant changes in the histopathology between HCV positive and negative cases.

According to the histo-pathological findings in current study, 17 patients (85%) had leukocytoclastic vasculitis, 3 patients (15%) had lymphocytic vasculitis.

In 1999 Ibrahim et al. [10] revealed lymphocytic vasculitis in (42.9%) of the HCV patients and leukocytoclastic vasculitis was evident in (57.1%) HCV patients.

As regard PAS stain of the skin biopsies, in this study 2 cases were positive for deposition of amorphous PAS substance, which suggest the possibility of being cryoglobulinemic.

The results of this study show that there are no significant differences between patients with cutaneous vasculitis lesions either with HCV positive or negative, as regard the liver function tests. This is agreed by Ibrahim et al. (1999**)** [10]as they reported that there does not appear to be a correlation between HCV infections and elevated ALT levels, they supported that cutaneous vasculitis has been reported as the initial manifestation of hepatitis C and the activity of vasculitis does not necessarily correlate with the activity of the patient's hepatitis.

On the other hand, ALT and AST levels were higher than normal in patients with HCV and LCV [14.]

The role of HCV in the development of cutaneous vasculitis is believed to be due to an immune process, it is suggested that immune stimulation of T-cell clones in HCV infection produces monoclonal macroglobulins with coaffinity to a constituent of HCV and IgG. Potential antigens of relevance include bacteria, viruses, drugs and other chemicals. Immune complexes have a role in HCV induced vasculitis and in cryoglobulinaemic vasculitis .[19]

HCV is a lymphotropic as well as a hepatotropic virus. Thus, the higher serum HCV viral load could lead to viral-dependent proliferation of B lymphocytes with subsequent increased formation of immunoglobulins, immune complex formation, and deposition in blood vessels walls, resulting in vasculitis [24]

From the available data shown in the present study, in comparison to other studies in different countries, we conclude that HCV may be one of the precipitating factors of cutaneous vasculities in those who have tendency to develop cutaneous vasculities, through its direct activation of T-cell to increase cytokine production.

As most of cases proved to be HCV positive in the studied patients, were not complaining of any apparent liver disease. It is recommended to exclude HCV infection in any case of cutaneous vasculitis either visit the dermatology clinic or detected by an Internist in a routine clinical examination.

In conclusion, hepatitis C virus infection is endemic in Egypt and cutaneous vasculitis has been reported as the initial manifestation of hepatitis C viral infection. Our purpose is to examine the skin as a mirror to detect internal diseases as early as possible. This study showed that the presence of cutaneous vasculitis should suggest to the Internist as well as the dermatologist that a hepatitis C virus may be a possible etiological or provocative agent. Such patients should be monitored with serum HCV antibodies and liver function tests for early detection and prevention of possible liver damage.

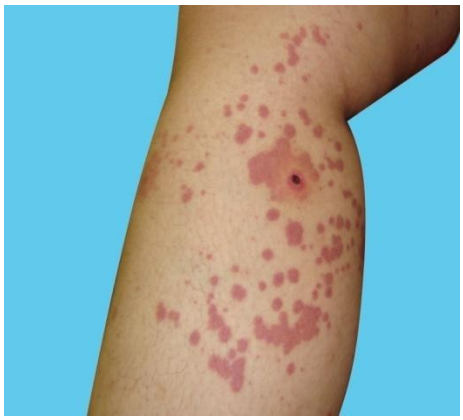

Fig. (1-A) leukocytoclastic vasculitis (LCV) of 24 years old female showing palpable purpura on both lower limbs. Serum HCV Ab was positive

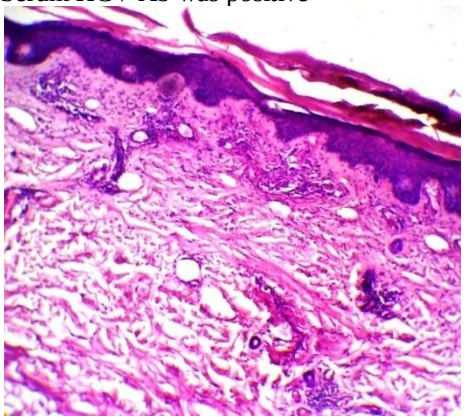

Fig. (1-B) Histopathology of the same ptient showing perivascular inflammatory infiltrate (H & E X 100).

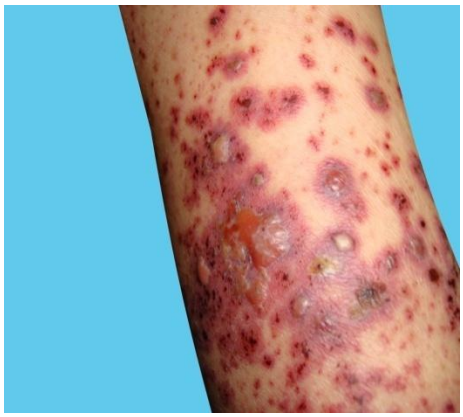

Fig (2-A) leukocytoclastic vasculitis (LCV) of 65 years old female showing palpable purpura and haemorragic bullae. Serum HCV Ab was positive.

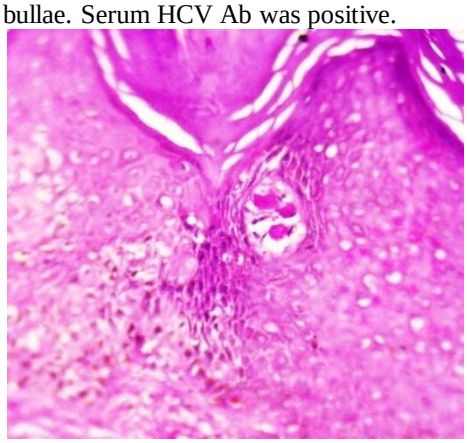

Fig. (2-B) Histopathology of the same patient showing deposition of amorphous eosinophilic material in lumen of blood vessel of the papilary dermis (PAS X 400).

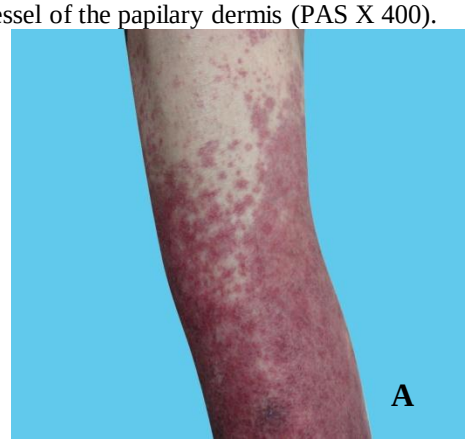

Fig. (3-A) leukocytoclastic vasculitis (LCV) of 44 years old male showing palpable purpura and ecchymosis on lower limb. Serum HCV Ab was positive.

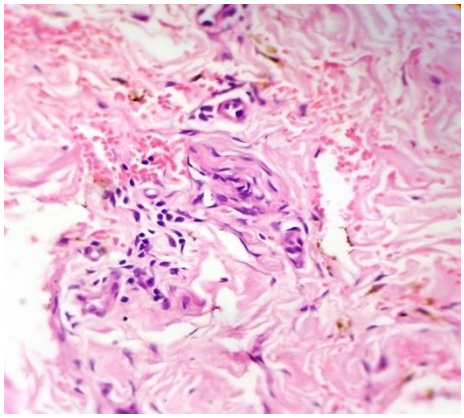

Fig. (3-B) Histopathology of the same patient showing inflammatory cells, hemorrhage, hemosiderin and some capillaries are lined by plump endothelial cells (H & E X400)

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