

Deep Vein Thrombosis - A Complication of Rickettsial Fever

Dr Rajesh M Honnutagi¹, Dr K Sugunakar Reddy², Dr M S Biradar³,
Dr Shankargouda S Patil⁴

¹Professor, Department of General Medicine, ²Resident, Department of General Medicine,
³Professor, Department of General Medicine, ⁴Associate Professor, Department of General Medicine
Shri B M Patil Medical College, BLDE (Deemed to be University), Vijayapura, Karnataka, India.

Corresponding Author: Dr Rajesh M Honnutagi

ABSTRACT

Rickettsioses are emerging infectious diseases which are debilitating and difficult to diagnose and are prevalent in some of the states of India. Here we present a rare and late hematological complication in a case of treated rickettsial encephalopathy.

Keywords: Rickettsioses, endothelial injury, coagulopathy, thrombosis.

INTRODUCTION

Rickettsioses are emerging infectious diseases and are being increasingly recognized in India. "Rickettsial diseases are reported in India since the 1930s with reports of scrub typhus from Kumaon region. [1] Rickettsioses, of which scrub is the commonest, has been reported in Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Bihar, West Bengal, Meghalaya, Rajasthan, Maharashtra, Karnataka, Tamil Nadu and Kerala states in India". [1] Rickettsial fevers are incapacitating and are difficult to diagnose in acute presentation owing to similar presentation, though can be treated easily, in case of diagnostic delays and untreated cases mortality ranges from 30-35%. [2]

Rickettsiae are a heterogenous group of "obligate intracellular, gram negative coccobacilli, which are transmitted by a tick, mite, flea, or louse vector". Among rickettsiae, *Coxiella burnetii*, *Rickettsia prowazekii*, and *Rickettsia typhi* will survive for prolonged period outside the reservoir or vector and are extremely

infectious. Scrub typhus, murine flea-borne typhus, Indian Tick Typhus and Q fever are common in India. [1] "The clinical manifestations of acute presentations are similar during the first 5 days: fever, headache, myalgias with or without nausea, vomiting, and cough. As the disease progresses, clinical manifestations may include a macular, maculopapular, or vesicular rash, eschar, pneumonitis and meningoencephalitis, hypotension with multiorgan failure varying one disease from the other depending on the species". [3] Etiologic diagnosis of rickettsioses is difficult in the acute presentations of illness because of similarity of manifestations and diagnosis requires the serological examination in the acute and convalescent phases. [4]

Rickettsial infection undergoes transovarian transmission from one generation of ticks to the next, and uninfected ticks get infected by feeding on rickettsemic mammal or feeding adjacent to infected tick. [5]

R. rickettsii organisms are inoculated into the dermis along with secretions of the tick's salivary glands after feeding. The rickettsiae spread through lymph and blood, infect many foci of contiguous endothelial cells. [6] The dose-dependent incubation period is approximately 1 week (2 to 14 days).

Thrombotic occlusion causing ischemic necrosis is not the primary pathological mechanism responsible for tissue and organ injury but the increased vascular permeability, resulting in edema, hypovolemia, and ischemia, is responsible for the organ damage. Thrombocytopenia (secondary to platelet consumption) is common, but disseminated intravascular coagulation with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system occurs as a homeostatic response to endothelial injury. [7]

"Rickettsia rickettsii and R. conorii have a propensity for the infection of endothelial cells of small vessels of skin, central nervous system, lung, myocardium, kidney, and liver". Endothelium has potent anticoagulant properties and any injury to endothelium alters the efficiency of anticoagulation property. Injury to endothelium, by apoptosis exposes membrane phosphatidylserine which leading to activation of factor X by factor IX. [7] "Apoptosis of endothelial cells leads to exposure of procoagulant subendothelial matrix, with or without cell detachment, and through cell retraction, apoptotic leukocytes and endothelial cells circulate as procoagulant bodies". Changes in endothelium following infection are associated with activation of the coagulation system. [7]

CASE REPORT

A 24 year old male computer operator in a private firm presented with high grade fever since 2 days associated with severe headache, giddiness and 3 episodes of convulsions since one day. On

examination hyperemic rash over the arms, chest and abdomen is found and other general physical examination and systemic examination was unremarkable. On investigations in complete blood count, total leucocyte count was found to be 13020 cells/cumm, with neutrophil predominance of 70.3%, platelet count is 1.47 lakhs/cumm, arterial blood gas analysis, liver function test, renal function test, and serum electrolytes were found to be within normal limits, urine routine test are found to be in normal limits, dengue serology for antibodies are negative, weil felix test is reported to be positive for rickettsial infection with significant OX19 antigen titres being 1:160. Patient is diagnosed with rickettsial encephalopathy and treated with doxycycline 100mg twice daily for 10 days and chloramphenicol 500mg intravenous twice daily for 5 days. Patient improved and discharged after a hospital stay of 12 days with no convulsions and febrile episodes during the last 5 days of hospital stay and is scheduled for review after 15 days of discharge.

Patient presented to our outpatient department on 16th day after discharge, for review with swelling of left foot, ankle and leg extending up to knee (figure 1) associated with mild pain and was tender on palpation. There are no engorged veins, no local rise of temperature. Patient is subjected to venous Doppler study and is reported to be having deep vein thrombosis with superficial thrombophlebitis involving, common femoral, superficial femoral, popliteal, short saphenous veins, with diffuse soft tissue edema in leg (figure 2, 3, 4, 5) and foot regions in left lower limbs. Homocysteine levels, protein c and protein s levels and activity are found to be in normal limits. Patient was put on unfractionated heparin infusion and later started on oral warfarin and review Doppler study was done and is reported the regression in the extent of deep vein thrombosis, patient improved symptomatically and is in regular follow up consultations.



Figure 1: Left leg swelling



Figure 5: No flow in superficial femoral vein.



Figure 2: Occlusion of popliteal vein



Figure 3: Doppler study showing common femoral vein obstruction



Figure 4: Doppler study showing soft tissue edema.

DISCUSSION

Rickettsiae are intracellular bacteria living in the cytosol of infected cells. The endothelium is target of rickettsiae and infection results in vascular injury to small blood vessels resulting hematologic manifestations like thrombocytopenia, increased concentrations of fibrinogen and von Willebrand factor in plasma, and activation of coagulation, resulting in consumption coagulopathy. The occurrence of deep venous thrombosis seems to represent a specific clinical feature of MSF among rickettsioses. [8]

Vasculitis results in “skin rash, microvascular leakage, edema, and tissue hypoperfusion and end-organ ischemic injury”. Formation of thrombi leads to tissue infarction and hemorrhagic necrosis. Rickettsial infective vasculitis may manifest as “interstitial pneumonitis, non-cardiogenic pulmonary edema, cerebral edema and meningoencephalitis”. [2]

In antithrombotic activity of endothelium, the protein C thrombomodulin pathway is of great importance. Endothelium expresses thrombomodulin, a surface glycoprotein, a receptor for thrombin. Thrombin bound to thrombomodulin activates the protein C - protein S pathway, Cytokines, which leads to inactivation of factors Va and VIIIa. Antithrombotic property of endothelium is altered with introduction of inflammatory mediators, vascular injury, infection (viruses) and endotoxins. Interleukin 1 and infections by viruses can induce the expression of procoagulant tissue factor, a

complex of glycoprotein and phospholipids, which is not constitutively expressed on the surface of Endothelium. Tissue factor bound to factor VII activates factor X, initiating the extrinsic pathway of coagulation. [8] In vitro infections by *R. conorii* and *R. rickettsii* have shown to induce injure endothelium and alter metabolic and secretory functions of endothelium, leading to increased secretion of fibrinolytic system factors (mainly plasminogen activator inhibitor 1) and an increase in platelet adhesion. Release of VWF multimers from Weibel- Palade bodies has been reported for endothelial cultures infected by *R. rickettsii*.

Rickettsial infections are vasculotropic diseases, often associated with haemostatic disturbances, which are more intense in patients with severe diseases. [8]

Though it is very rare that patient developing deep vein thrombosis in rickettsial infection, there are reported cases where, rickettsial infection leading to hypercoaguable state leading to DIC and DVT in severe infection cases during acute phase. In our present case in discussion the patient did not develop any haemostatic disturbances in acute phase and during 12 days of hospital stay, but during follow-up after 15 days of discharge patient presented with pedal edema having deep vein thrombosis. Although keeping in mind about the rarity of complication in rickettsial fevers, the gravity of potential morbidity and mortality and potential possibility of prevention and treating the condition, it is always prudent to include deep vein thrombosis in the differential diagnosis and possible complications when in hospital stay as well as after discharge and counseling the patient for the need for regular follow-ups and educating the patients at discharge regarding red flag symptoms and signs for timely consultation and seeking advice after

discharge. This case reminds the importance of follow-ups after complete recovery from acute phase of disease.

CONCLUSION

As Rickettsial fever are emerging infections and there is every chance of missing the diagnosis due to nonspecific presentation, and treatable causes of life threatening complications, we suggest it is prudent to have these complications of late haemostatic disturbances like deep vein thrombosis in thought while discharging the patient and counseling the patient for regular follow ups to prevent patient suffering from any morbidity and mortality which is completely treatable with timely approach and intervention.

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How to cite this article: Honnutagi RM, Reddy KS, Biradar MS et.al. Deep vein thrombosis - a complication of rickettsial fever. International Journal of Research and Review. 2019; 6(8):177-180.
