Blood culture- negative Infective endocarditis presenting with atypical dermatologic manifestation: a rare case report and review of the literature

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Abstract

Infective endocarditis rarely presents with cutaneous manifestations due to earlier diagnosis and treatment. We present a case of a middle-aged male patient presenting with an erythematous papular rash in the upper extremities and left knee, further progressing into painful ulcers.

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Introduction

Infective endocarditis (IE) is characterized by inflammation of the endocardium, including the endocardial wall and heart valves (1). Blood culture-negative endocarditis (BCNE) is marked by probable or definite endocarditis where three or more blood cultures sampled over 48 hours are negative despite adequate incubation(> I week). It accounts for 2.5% to 31% of all cases of IE(2) . Major causes of BCNE include: 1) Antibiotic administration prior to sampling (often due to infection with prevalent causative organisms, such as*streptococci* , *staphylococci* , or *enterococci*), 2) presence of fastidious organisms, which are hard to culture. These include *Propionibacterium acnes* , *HACEK* bacteria, defective *streptococci* - *Gemella* , *Abiotrophia* sp.,*Granulicatella* and *Candida* . 3) the "true" BCNE due to infection with intra-cellular organisms that may not be typically cultured using conventional techniques (usually due to infection with*Bartonella* or *Coxiella burnetti*) (3).

IE occurs most commonly in susceptible patients with prosthetic heart valves, unrepaired cyanotic congenital heart diseases, rheumatic fever, intracardiac devices , previous IE and history of intravenous drug use. Nonetheless, approximately half of the affected patients have no associated risk factor (4).

IE often presents with symptoms of multi-organ involvement. Dermatologic manifestations of IE include Osler's nodes, Janeway lesions, cutaneous infarcts and petechiae, which usually manifests later in the disease course. Although skin manifestations are important in evaluating patients with infective endocarditis, few studies in the literature evaluated their importance in the disease manifestation and the diagnostic dilemma associated with atypical presenting symptoms.

This paper presents a case of IE with atypical skin manifestations and reviews the major skin findings in the affected patients.

Case presentation

The patient is a 58-year-old man with a medical history of type 2 diabetes mellitus and ischemic heart disease with recent acute myocardial infarction and primary cutaneous intervention (PCI) who presented to the emergency department with abrupt onset of shaking chills associated with fever and drenching sweats. The day prior to admission, the patient had similar symptoms, for which he received intravenous anti-pyretics in a primary urgent care centre. In addition, he complained of an erythematous papular rash starting 10 days prior to admission, which had initiated from the right arm and forearm and further progressed to involve the bilateral upper extremities, anterior aspect of the left knee and fingers of the both hands. After 7 days, these lesions had progressed into painful ulcers with crusted and necrotic center without associated purulent discharge, especially in the arms and fingers. The patient did not seek any medical care for these skin lesions. In addition, he also suffered from an episodic, retrosternal chest discomfort for one week. Social history was significant for exposure with poultry. The patient was a life-time non-smoker and did not use illicit or recreational drugs.

Upon arrival, the patient was alert, oriented and toxic-appearing with blood pressure of 103/56 mmHg, temperature of 38.5°C, heart rate of 78 beats/min and respiratory rate of 17/min. Physical examination of the skin revealed numerous erythematous papules and plaques of 1*1to 2*2 cm mainly located on the extensor aspect of the right forearm, anterior aspect of the left knee and first finger of the left hand. These lesions had an erythematous rim and central, necrotic crusts in association with a mild purulent area surrounding the crusted zone. There were no purulent discharges and the lesions were extremely tender to minimal palpation. Since the patient was initially admitted in the emergency department, no picture of the initial lesion is present. His cardiac examination showed a regular rhythm and rate with no murmurs. The remainder of the physical examination was normal.

Laboratory evaluation demonstrated no significant leukocytosis but an elevated ESR (erythrocyte sedimentation rate) and CRP(C-reactive protein). The results of the complete metabolic panel were within the normal ranges. Serial troponin and Ekg monitoring were normal. Chest X-ray revealed no abnormality. Blood cultures acquired initially were negative. Infectious disease consultation was obtained and intravenous antibiotics (levofloxacin+imipenem) were administered to treat the probable pseudomonal –related sepsis due to probable ecthyma gangrenosum. Fever was subsided and skin rash was improved following administration of antibiotics. During the course of hospitalization, three separate sets of blood cultures were obtained and turned negative.

Dermatology consultation was performed and smears of the lesions were obtained and cultured to evaluate cutaneous leishmaniasis, gram positive organisms including *Streptococci* , *Bacillus anthracis* and fungal infections. Since the patient was from an endemic region for malaria and leishmania infection, the peripheral blood smear was evaluated for malaria and leishmania parasites. Intravenous levofloxacin was exchanged for oral levofloxacin. The gram smear of the lesion demonstrated gram-positive cocci with polymorphonuclear cells with no fungi, bacillus or leishmania bodies. Culture of the lesion turned negative after adequate incubation. On the 7^{th} day of admission,the fever relapsed. Covid-19 PCR was obtained and turned positive. As a result, early treatment with remdesivir was initiated, levofloxacin was discontinued and intravenous

vancomycin was instilled. The patient developed new erosive oral enanthems and smaller lesions similar to the primary manifestation, most commonly on the fingers and the left knee (Figure 1). Considering this and the recently-diagnosed Covid-19 infection, the cutaneous lesion of knee was biopsied. Subsequently, the patient complained of intermittent, short-lasting, squeezing chest discomfort accompanied by mild dyspnea. Serial Ekg monitoring and blood troponin levels were normal .Cardiology consult was re-evaluated and TTE (transthoracic echocardiography) demonstrated normal LV (left ventricular) systolic function, mild LV diastolic dysfunction , 1+ tricuspid valve regurgitation , mild mitral regurgitation and vegetation-like lesions on the surface of mitral valve leaflets(Figure2) . Meanwhile, repeated blood cultures turned negative . A previous TTE from 3 months earlier revealed no abnormality, despite mild LV diastolic dysfunction following acute myocardial infarction. The result of the skin biopsy revealed perivascular inflammatory infiltrates, predominantly polymorphonuclear cells and lymphocytes in combination with extravasated red blood cells and fragmented nuclear debris, consistent with cutaneous leukocytoclastic vasculitis (Figure3).

The patient was subsequently diagnosed with possible subacute bacterial endocarditis based on the modified Duke criteria for infective endocarditis; as having endocardial involvement as the major clinical criteria and fever, vascular phenomena as the minor criteria. The skin lesions were likely due to septic embolization and deposition of circulating immune complexes with the resultant leukocytoclastic vasculitis. Antibiotic therapy was continued and the patient's symptoms improved remarkably and he was finally discharged home with stable vital signs.

Discussion

Infective endocarditis (IE) may lead to life-threatening complications. The incidence of IE has changed widely in the last decade, with a significant rise particularly in the developing countries (5).Symptoms of IE are caused by a variety of mechanisms: a) direct local destruction of the involved endocardial surfaces, b) hematogenous dissemination to other tissues, c) metastatic embolization of fragments to other organs, and d) formation of immune complexes and precipitation in the distant sites. IE is currently diagnosed based on the modified Duke criteria, with a sensitivity of 80% and specificity of 99%,however its diagnosis may be delayed due to the wide range of non-specific symptoms (6). In the developed countries, *Staphylococci* has become gradually as the most frequent pathogenic organism isolated in infective endocarditis, possibly due to increased rate of intravenous drug use or advanced hemodialysis ,whereas *Streptococci* accounts for the majority of cases in the developing countries(7, 8). Rate of positive blood cultures in patients with infective endocarditis ranges between 83 to 96% in developed countries (9).Extensive administration of antibiotics prior to sampling may contribute to the low rate of microbiological detection in BCNE, particularly due to gram-positive cocci. Installation of specific PCR (polymerase chain reaction) tests depending on the geographic distribution pattern of most common causative organisms, may yield a higher detection rate (10).Likewise, our patient had negative blood cultures on serial sampling, possibly due to consumption of antibiotics prior to referral to our hospital.

Infective endocarditis may present with skin lesions in approximately 5% to 25% of affected patients. The most commonly reported cutaneous lesions include purpura, followed by Osler nodes and Janeway lesions in decreasing order of frequency. Purpura are more commonly found on the lower extremities(11).The incidence of Osler nodes and Janeway lesions have reduced significantly in the recent years, changing from 10–23% in the 1980s to $<$10% for Osler nodes and ranging between 1.6% -4.7% for Janeway lesions(12). This decline is likely due to earlier diagnosis of IE and installation of treatment, which does not allow the formation of skin lesions (11). Based on the modified Duke criteria, Osler nodes and Janeway lesions are considered immunologic phenomena and vascular phenomena; respectively, however, both these lesions have similar pathogenesis, with septic microemboli lodging in vessels, leading to the activation of pro-inflammatory cytokines. In addition, immune-mediated vasculitis has been also found in the pathogenesis of Osler nodes. Histopathologic examination of both lesions demonstrates septic microemboli with necrotic dermal micro-abscesses (13).Osler nodes are characterized clinically as tender, subcutaneous , violaceous nodules most frequently located on the toes and fingers and to a lesser degree on the lateral digits, thenar and hypothenar region. On the other hand, Janeway lesions are marked by irregular, non-tender, erythematous or hemorrhagic nodules or

macules, often found on the palms (12).

Cutaneous leukocytoclastic vasculitis is characterized by vasculitis of small-sized, dermal capillaries and venules. It may occur as a result of autoimmune disorders, drug reactions, malignancy and infections. Clinically, it manifests as erythematous, palpable purpura on the dependent lower extrimities. Most common infectious causes of leukocytoclastic vasculitis include *streptococci* and*staphylococci* (14). Cutaneous leukocytoclastic vasculitis as the the presentation of infective endocarditis has been reported well in the literature. It is likely due to the deposition of circulating immune complexes and emboli on the vascular endothelial surface(15) .Moreover, cutaneous leukocytoclastic vasculitis may be associated with deposition of IgA in various organs, specifically the kidneys , resulting in varying degree of proteinuria, hematuria or renal failure and IgA glomerulonephritis in the renal biopsy(16).In our patient, although the lesions were not typical of leukocytoclastic vasculitis, the histologic examination was consistent with cutaneous leukocytoclastic vasculitis , and the gram smear of the lesion showed gram-positive cocci , excluding other non-infectious causes, highlighting an underlying infectious disorder as the culprit of his skin finding , which in association with his other clinical symptoms (dyspnea, chest pain) raised suspicion for infective endocarditis. Of note, skin manifestations carry poor prognosis in infective endocarditis, as they are associated with an embolic process (11).

Complex percutaneous coronary intervention (PCI) requires installation of numerous devices into the arterial circulation, which increases the likelihood of bacteremia or septicemia. In a study of Ramsdale et al., 17.7% of patients undergoing complex PCI developed bacteremia immediately following PCI, with the *coagulase-negative staphylococci* being the most commonly isolated organism and 12% developed positive blood cultures within 12 hours post-PCI. Interestingly, no clinical sequelae developed (17). Our patient had a recent history of PCI 4 weeks prior to admission. This hint in association with gram-positive cocci in the gram smear of lesions and resolution of lesions following administration of vancomycin , implicates c*oagulase-negative staphylococci* as the causative organism.

Our case displays the cutaneous manifestations of IE as the presenting symptoms in the absence of other more common features. Hence, clinicians must carefully assess for skin manifestations in borderline scenarios, as skin involvement often conveys worse outcomes.

Conclusion

Our case depicts atypical presentations of IE that may complicate the initial diagnosis.It is noteworthy for physicians to investigate for the skin lesions of IE, particularly when the diagnosis is not definite.Skin manifestations implicate an increased risk of embolic complications, thus delayed diagnosis may be life-threatening.This further necessitates the importance of thorough physical examination for physicians.

Keywords: Infective endocarditis, skin, cutaneous leukocytoclastic vasculitis , PCI

Availability of data and materials

The datasets during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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Competing interests

No competing interests .

Conflict of Interest

All co-authors contributed significantly to this study.MM, JA,MS collected images . Design of the study was conceptualized by MM,JA. The initial draft of the manuscript was written by FD,SMM. Final version of the manuscript was edited by MM,FD. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

Consent for publication

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Legends of descriptive:

Figure 1

Round, well-circumscribed ulcers with erythematous border and necrotic central zone.

Figure 2

Small, vegetation-like particles are evident on the surface of mitral valve leaflet.

Figure 3

Skin biopsy of the knee lesions. Perivascular inflammatory infiltrates , mainly composed of neutrophils and lymphocytes in association with extravasated red blood cells and fragments of the nuclear debris.