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**CASE REPORT**

# Acute Rheumatic Fever (ARF) in a patient of Chronic Mucocutaneous Syndrome or Mucocutaneous Candidiasis having Diarrhea and Skin Rash

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## SUMMARY

Acute Rheumatic fever (ARF) is the most common cause of acquired heart disease in the developing world. It is an immunological reaction to group A beta-hemolytic streptococcus Pyogenes. It occurs 2-4 weeks after group A streptococcal pharyngitis due to the development of antistreptococcal antibodies that cross-react with antigens in various tissues of the body, especially cardiac and basal ganglia neuronal antigens. Clinical features of acute rheumatic fever include fever, joint pain, myocarditis, nodules in subcutaneous tissue, Erythema Marginatum, and chorea. Patients with immunodeficiency like mucocutaneous candidiasis are especially prone to recurrent mucocutaneous infections (tonsillopharyngitis, thrush, skin abscess), which can predispose to acute rheumatic fever and subsequent development of rheumatic heart disease over the years.

**Keywords:** Acute rheumatic fever, chronic mucocutaneous syndrome, skin rash,

## INTRODUCTION

A chronic mucocutaneous syndrome is a heterogeneous group of disorders characterized by chronic non-invasive candida infections involving skin, mucus membranes, hairs, and nails, along with autoimmune manifestations commonly involving the endocrine system, with primary hypoparathyroidism and Addison's disease being the most prominent. Problems with IL-17 signaling are usually present in patients with chronic mucocutaneous syndrome[1]. Abnormally functioning T-cells and decreased number of immunoglobulins can also result in chronic mucocutaneous syndrome. Patients present with oral thrush, esophagitis, dermatitis, hair loss, and infections of nail[2]. This disease is diagnosed based on clinical manifestations. However, diagnosis can be aided by the presence of yeast cells and pseudohyphae on skin swab preparations [3]. Confirmatory diagnosis involves identifying disease-causing various genetic mutations. The primary treatment for this disease is antifungal medications and the management of any endocrine disorder if present[4].

## CASE PRESENTATION

This case report presents an atypical association of acute rheumatic fever (myocarditis and valvulitis in particular) in a patient with the chronic mucocutaneous syndrome. A 9-year-old boy was suspected of having chronic mucocutaneous candidiasis with myocarditis based on presenting signs and symptoms. However, further testing revealed he has been suffering from acute rheumatic fever with severe left ventricular systolic dysfunction, pericardial effusion, and possibly severe mitral valve insufficiency.
**Conclusion:** Therefore, it is of utmost importance that clinicians be aware of this association between immunodeficiency diseases and acute rheumatic fever, which could result in timely and effective management of group A streptococcal pharyngitis to prevent the development of acute rheumatic fever. There should be a low threshold of suspicion for acute rheumatic fever in immunodeficient populations presenting with cardiac signs and symptoms.

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Hypoparathyroidism is the most common endocrine disorder in these patients, which can cause hypocalcemia and hypomagnesemia, sometimes leading to tetany and seizures.

Symptoms like rash and fever are common in chronic mucocutaneous syndrome and rheumatic fever. The diagnosis of rheumatic fever requires 2 major criteria or 1 major plus 2 minor criteria. Major criteria (aka Jones Criteria) of rheumatic fever include polyarthritis, carditis, subcutaneous nodules, erythema marginatum, and Sydenham chorea; while minor criteria include fever, increased levels of C-reactive protein, and/or erythrocyte sedimentation rate, increased PR interval and past medical history of rheumatic fever [5]. This article presents a unique case of chronic mucocutaneous syndrome in a 9-year-old boy who initially presented with fever, diarrhea, alopecia, rash, chest pain, and tetanic spasms but was ultimately diagnosed with rheumatic fever on further workup.

## CASE PRESENTATION

A 9-year-old boy presented with the chief complaints of fever, diarrhea, alopecia, rash, chest pain, and tetanic spasms for the past three months. According to the patient attendant, the patient had multiple episodes of loose, watery stools per day. He had no history of oral ulcers, fissures, and lymphadenopathy. There was no family history of cardiac disease, deafness, seizures, and sudden infant deaths of his siblings. He was born at full term through normal vaginal delivery in the hospital and had no birth anomalies. He started sitting at 8 months of age and walking at 1 year of his age. Further developmental history revealed a developmental delay in speech. He had three other siblings, who were normal. Vitals on admission were as follows: oxygen saturation was 96%, blood pressure was 95/60 mm of Hg, and pulse was 115 beats per minute with regular rhythm and good volume. Physical examination revealed an active boy with no abnormal findings except a rash on his face. Laboratory investigations are shown in table 1. Echocardiography showed severe left ventricular dysfunction with pericardial effusion (Fig 1). A chest x-ray was also done, revealing a globular heart (Fig 2). The patient was subsequently put on decompensated heart failure medications and antibiotics to eradicate the possibility of group A streptococcal colonization (Table 2).

### Laboratory Investigation findings:

Table 1: Laboratory workup of patient at initial presentation.

| Name of Investigation | Results | Normal Range | Unit |
|---|---|---|---|
| Hemoglobin | 13.1 | M=14-18<br>F= 11.7-15.7 | g/dl |
| W.B.C | 12.0 | 4.0-10.0 | X10/L |
| Neutrophils | 77 | 40-70% | |
| Lymphocytes | 17 | 20-25% | |
| Monocytes | 04 | 2-10% | |
| Eosinophils | 02 | 1-2% | |
| Platelets Count | 360 | 150-400 | X10/L |
| Sodium | 142.0 | 136-149 | mmol/L |
| Potassium | 3.9 | 3.8-5.2 | mmol/L |
| Chloride | 103.0 | 98-107 | mmol/L |
| Random Blood Sugar | 182 | 80-140 | mg% |
| Blood Urea | 21 | 10-50 | mg% |
| CRP | positive | | |
| Serum Calcium (Total) | 6.5 | 8.8-12.0 | mg/dl |
| Serum Calcium (Ionized) | 2.7 | 4.4-5.2 | mg/dl |
| PTH-Intact | 6.01 | 15-65 | pg/ml |
| Anti-Streptolysin "O" | 315 | 0-150 | IU/ml |
| Highly Sensitive Troponin-I | 50.0 | 0-33 | ng/L |
| Antinuclear Antibody | 0.30 | <1.0 | |
| Physical Examination of Stool | | | |
| Color | Yellowish | | |
| Color | Yellowish | | |
| Reaction | Acidic | | |
| Consistency | loose | | |
| Blood | NIL | | |
| Mucus | NIL | | |
| **Microscopic Examination of Stool** | | | |
| Ova | Not Seen | | |
| Cyst | Not Seen | | |
| Pus Cells | 04-05 | | |
| RBCs | NIL | | |

WBC: whole blood cells; CRP: C-Reactive protein; RDW: red cell distribution width; PTH: parathyroid hormone; RBC: red blood cells; mmol/L: millimoles per liter.

### Echocardiography:

Figure 1 Transthoracic Echocardiographic Images showing significant pericardial effusion (white arrow) with severe left ventricular systolic dysfunction possibly due to myocarditis.

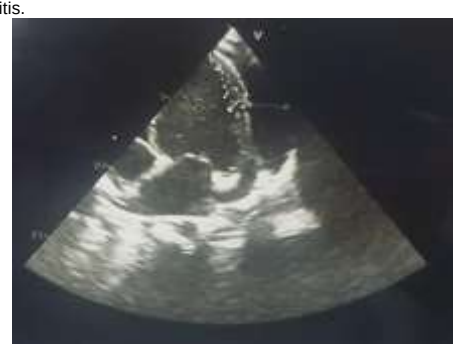

Figure 2 Chest X-ray of patient revealing globular heart (black outline) due to pericardial effusion and myocardial dysfunction. The left cardiac silhouette is enlarged.

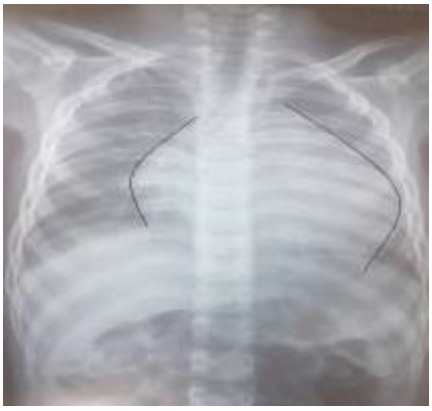

Table 2: Medications given at the hospital and home.

| Name of a drug | Route of administration: | Dosage | Duration |
|---|---|---|---|
| Inj. Cefoperazone-sulbactam | Intravenous | 250 mg | B. D |
| Inj. Furosemide | Intravenous | 2 cc | B. D |
| Tab. Captopril | per oral | 125mg | T.D. S |
| Inj. Calcium Gluconate in 100ml pladex | Intravenous | 20 cc | T.D. S |
| Atem and Clinil nebulization | Inhalational | 2cc | QID |
| **Home treatment** | | | |
| Syp. Motilium (antiemetic) | per oral | 3cc | T.D. S |
| Syp. Hydrillin (antitussive) | per oral | 2cc | B. D |
| Tab Spironolactone | Per oral | 50 mg | B. D |
| Syp Cefixime | per oral | 250mg | B. D |

Abbreviations: TDS: thrice daily; BD: twice daily; QID: 4 times daily; mg: milligram; cc: cubic centimeter.

## DISCUSSION

Chronic mucocutaneous candidiasis is an immune deficiency syndrome affecting the skin, nails, mucous membranes of lungs, and gastrointestinal tract and is associated with endocrine disorders [6]. Other manifestations are autoimmune hemolytic anemia, autoimmune neutropenia, autoimmune thrombocytopenia, alopecia areata, chronic diarrhea, and rheumatoid arthritis. The neutropenic and non-reactive lymphocytic state in chronic mucocutaneous candidiasis makes the patient prone to bacterial and fungal infections. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED aka APS 1 autoimmune polyglandular syndrome type 1) is syndromic chronic mucocutaneous candidiasis caused by autoimmune regulator (AIRE) deficiency which is responsible for clonal destruction of autoreactive T cells in the thymus. Without it, autoreactive T cells are free to enter the bloodstream and cause various autoimmune diseases like Addison disease, primary hypoparathyroidism, hypothyroidism, alopecia areata, and type 1 diabetes mellitus[7]. Due to defective T cell signaling, they are prone to chronic non-invasive candida infections and attenuated response to candida skin antigen test. Diagnosis is generally clinical, whereas treatment focuses on oral fluconazole therapy for treating candida infections and is chronically used to suppress its regrowth [1].Ketoconazole has also been reported to effective in patients of Chronic mucocutaneous candidiasis[8]. Among the clinical features of Chronic mucocutaneous candidiasis described above, our patient had diarrhea, alopecia, and rash. Apart from this, the laboratory investigations also showed a picture of hyperparathyroidism as his PTH and serum ionized calcium were low.

The patients of Chronic mucocutaneous candidiasis can develop clinical or subclinical episodes of non-candida infections[8]. If an episode of untreated streptococcal pharyngitis occurs , it may result in an acute presentation of rheumatic fever with migratory polyarthritis, fever, rash, chest pain due to pericarditis, and in severe cases may cause acute heart failure due to combination of acute mitral regurgitation and myocarditis[9]. Inflammation can affect all layers of the cardiac wall, but endocarditis leading to valvulitis (mitral valve, aortic valve) is the most common cardiac

manifestation. A holo-systolic murmur at the cardiac apex of mitral regurgitation can be heard on the clinical exam. Sometimes a short mid-diastolic murmur (Carey Coomb murmur) is heard loudest at the cardiac apex; it is an indicator of moderate to severe mitral regurgitation because of increased blood flow across the mitral valve during left ventricular filling. Pericardial friction rub may be heard in case of pericarditis. Electrocardiography may reveal PR interval prolongation, and transient 1st and 2nd-degree heart block can occur in severe cases. Various heart wall layers (endocardium, myocardium, and pericardium) can be involved, causing myocardial dysfunction with pericardial effusion in some cases [10,11]. The clinical features and laboratory investigations suggestive of acute rheumatic fever in our patient included fever, chest pain, rash, pericardial effusion, and high levels of Antistreptolysin "O" antibodies.

Our patient had mixed clinical picture having clinical features of both chronic mucocutaneous candidiasis and acute rheumatic fever. Echocardiography is the diagnostic modality of choice in such mixed presentations as it can yield an early diagnosis of rheumatic fever with suggestive findings like mitral valve regurgitation, left ventricular volume overload with wall hypokinesis, and can then guide appropriate treatment saving the patient from detrimental consequences of severe disease. Prompt treatment with medications that reduce preload (diuretics), and afterload (angiotensin-converting enzyme inhibitors) will save the patient from heart failure. Penicillin or cephalosporins can be initiated to eradicate group A streptococcus[10]. Anti-inflammatory drugs like Non-steroidal anti-inflammatory drugs (naproxen, ibuprofen) can be administered for arthralgias and to suppress inflammatory mediators. Some clinicians also give steroids for severe disease presentations, but it is not recommended[12]. Later, when the patient is stabilized, mitral valve repair/replacement surgery can be considered for severe decompensation after a cardiology opinion [13]. Mitral valve repair is preferred over mitral valve replacement because it avoids lifelong anticoagulation therapy required for metallic valves, but the reoperation rate is more frequent with valve repair[14]. In addition, the most crucial part of treatment is to prevent future occurrence of acute rheumatic fever by secondary prophylaxis with Intramuscular Benzathine penicillin given monthly for a period depending upon the extent of cardiac involvement. Those with no cardiac involvement at initial presentation (on clinical exam and echocardiography) are given penicillin prophylaxis for a period of 5 years or until 21 years of age (whichever is longer), those who have cardiac involvement at initial presentation but no residual disease (on echocardiography) are given prophylaxis for 10 years or up to 21 years of age (whichever is longer), and those with cardiac involvement with residual disease (like mitral regurgitation) are given prophylaxis for 10 years or up to 40 years age (whichever is longer). This antibiotic prophylaxis limits the early development of rheumatic heart disease later in life[15].

## CONCLUSION

Rheumatic fever can occur in immunodeficiency syndromes like chronic mucocutaneous syndrome. If suspected, patients should be evaluated using antistreptolysin titers, chest x-ray, electrocardiograms, echocardiography, coronary angiography, and troponin I. Early diagnosis of rheumatic fever in chronic mucocutaneous candidiasis can aid in timely and effective treatment of any cardiac complication like acute heart failure and administration of antibiotics for eradication of group A streptococcal infection with the initiation of secondary prophylaxis for prevention of recurrent episodes of acute rheumatic fever. Thus, reducing the risk of progression towards rheumatic heart disease in the future and limiting morbidity and mortality in such disease-prone populations.

**Conflict of interest:** Nil

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