CASE REPORT

Disseminated tuberculosis in a patient with antinuclear antibody-negative systemic lupus erythematosus: a rare association

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SUMMARY

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse manifestations. Tuberculosis is known to induce and exacerbate SLE and it becomes quite difficult to diagnose tuberculosis in this setting, owing to a similar, overlapping presentation of tuberculosis and SLE. We report a case of disseminated tuberculosis in a patient with antinuclear antibody-negative SLE. Treatment was started with antitubercular drugs together with hydroxychloroquine and steroid. After 6 months of follow-up the patient recovered with treatment.

BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse manifestations. Studies have shown that infections can induce and exacerbate SLE. Tuberculosis (TB) is a common problem in developing countries like India. Its presentation often overlaps with an SLE flare. Management of the two conditions simultaneously is difficult, as steroids and immunosuppressive drugs can exacerbate TB. Antinuclear antibody (ANA) is a sensitive test used to screen for SLE and with the newer methods of detection, cases of ANA-negative SLE are rare. Our reported case is presented to discuss the interaction of TB with SLE and the rare entity of ANA-negative SLE.

CASE PRESENTATION

A 36-year-old woman presented who had had fever and cough for 3 months. The fever was moderate grade, intermittent and without chills. The cough was without expectoration or haemoptysis. On examination she had a low body mass index of 18 kg/m^2, and stable vital signs. She had pallor. A lymph node was palpable at the left upper jugular region, 3×2 cm, mobile and non-tender. A chest examination showed coarse crepitations in the left suprascapular and interscapular regions.

On investigation, her haemoglobin was 9 g/dl and microcytosis and hypochromia were shown on a peripheral blood smear. She had leucopenia (total leucocyte count 2900/µl) with normal platelet count (23010^9/l). Liver and kidney function tests were normal. Urinary albumin was 3+, but 24 h urinary protein was only 280 mg/dl. A skiagram chest image showed right perihilar fibrocalcific changes and left upper-zone fibronodular infiltrations. Sputum examination for acid-fast bacilli, and a Mantoux test were negative. Ultrasonography of the abdomen showed hepatosplenomegaly. Contrast-enhanced CT of the chest showed consolidation with conglomerate ill-defined nodules and ground-glass opacity in the left upper lobe; enlarged lymph nodes in the bilateral axillary nodes and supraclavicular regions, with few of these having central necrosis; multiple subcentimetric calcified nodes in the mediastinum (figure 1). Biopsy of the left cervical node showed fibrocaseous tuberculosis and an acid-fast bacilli test was positive.

On the basis of the above findings, a diagnosis of disseminated TB was made and antitubercular treatment (ATT) was started. Fourteen days after ATT, she developed rashes over the malar area and nose, not associated with pain, itching or swelling. These rashes were butterfly shape, flat, non-tender erythematous (figure 2). She also had a history of alopecia in the past month and joint pain for the past 3 months. Pain affected the small joints of both hands and knee joints and was not associated with redness, swelling or morning stiffness. Examination of the oral cavity was normal. Examination of the eye showed mild episcleral congestion with normal fundus. Other systems and joints were normal.

INVESTIGATIONS

To investigate whether the patient had SLE, a quantitative serum ANA (Hep 2) titre was determined and found to be 1/40 (negative). However, anti-double stranded DNA (anti-dsDNA; 182.92 IU/ml (<35)) and antihistone antibody (76.20 IU/ml

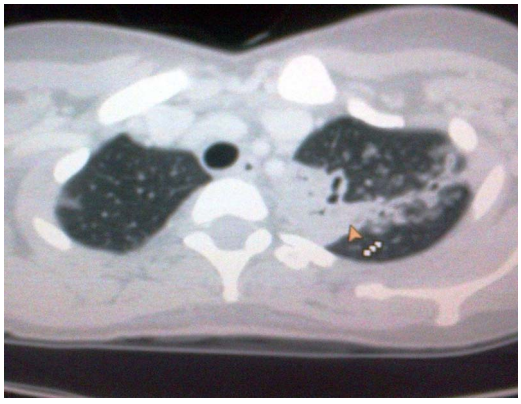

Figure 1 Contrast-enhanced computed tomography of the chest showing consolidation with conglomerate ill-defined nodules (arrow head) and ground-glass opacity in left upper lobe.

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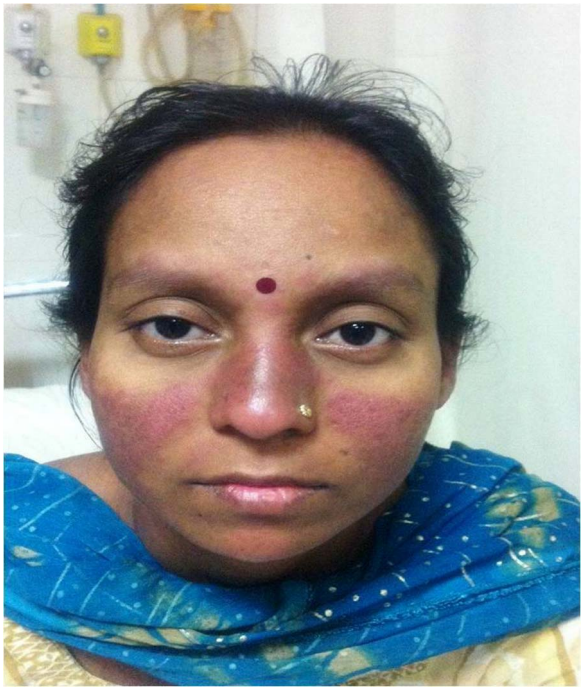

Figure 2 Malar rash: butterfly shape, flat, non-tender erythematous rash over cheek and nose.

(<15)) were raised. Anti-Smith antibody (anti-Sm antibody) was within the normal limit (7.59 U/ml (<10)). Serum C3 and C4 complement levels were reduced. Hand and knee radiographs were normal.

DIFFERENTIAL DIAGNOSIS

Disseminated tuberculosis with:

- ANA-negative SLE;
- drug-induced lupus erythematosus (DILE).

TREATMENT

We considered the patient to have disseminated TB with ANA-negative SLE (arthralgia, malar rash, alopecia, episcleritis, leucopenia, proteinuria (3+), raised anti-dsDNA antibody; fulfilling 5/11 American College of Rheumatology criteria[1]). Initially, isoniazide was stopped as DILE was suspected but it was restarted, and the patient received a full dose of antitubercular treatment. Hydroxychloroquine and steroids were given for SLE, and she was followed up closely.

OUTCOME AND FOLLOW-UP

After 6 months of follow-up, the patient was asymptomatic clinically and continued to receive immunosuppressive drugs.

DISCUSSION

Although there are no formal classification criteria for the diagnosis of DILE, it is widely accepted that it is the development of lupus-like symptoms (commonly, fever, musculoskeletal involvement and serositis) temporally related to continuous drug exposure (1 month), which resolve when the offending drug is stopped.[2] The time between drug exposure to onset of symptoms varies from 1 month to a decade or more after initiation of the drug treatment. The onset is generally insidious. It is usually accompanied by serological findings of a positive ANA titre and antihistone antibodies.

Our patient developed rashes after taking ATT for just 15 days and she had had symptoms suggestive of SLE (joint pain, alopecia) for a longer period of time. Moreover, the age of patient and other features of the patient favoured classic SLE as described in table 1.

Patients with SLE are prone to infections owing to abnormalities in their immune system: immunoglobulin deficiency, complement deficiencies, defects in chemotaxis, phagocytosis, delayed hypersensitivity and abnormalities of cellular immunity.[3] Infections such as TB are more common in patients with SLE owing to these abnormalities and the use of immunosuppressive drugs. Erdozain *et al*[4] in Spain, Mok *et al*[5] in Hong Kong, Gaitonde *et al*[6] and Agrawal *et al*[7] in India reported that TB was sixfold, 5–15-fold and 10–60-fold higher in patients with SLE than in the general population of respective countries.

Moreover, the disease is often more severe and disseminated in these groups of patients.[8] Mortality is often high owing to delay in diagnosis, immunosuppressive drugs and concomitant exacerbation of SLE. The two disease processes often mimic each other; symptoms of fever, malaise and weight loss are common in both conditions. Extrapulmonary TB is more common and presents with arthralgia, skin nodules and weight loss. Confirmation of a clinical suspicion of TB in a patient with SLE is difficult: miliary and extrapulmonary TB are difficult to confirm; presenting symptoms overlap with an SLE flare. Patients with lupus nephritis or a past history of TB infection are at increased risk of a new infection.[8]

Treating TB in a patient with SLE is also difficult. Studies have shown that patients with SLE who developed TB were receiving a higher dose of prednisone; Tam *et al*[9] found that for each gram of prednisolone, there was a 23% increased risk of developing TB. The treatment of TB in patients with SLE follows the same recommendations as those for other patients with this disease. Moreover, studies also have shown that TB may induce and exacerbate SLE.

The ANA titre is a useful test for screening for SLE. For diagnosis a positive test for a specific antibody is more important than is a negative ANA test. Thus an 'ANA-negative' person

Table 1 Comparison of classic lupus and drug-induced lupus

	SLE	Drug-induced lupus
Average age of onset (years)	20–30	50–70
Female-to-male ratio	9 : 1	1 : 1
Race affected	Blacks>Whites	Whites>Blacks
Clinical course	Chronic, relapsing	Remits with drug cessation
Symptom severity	Mild to severe	Generally mild
Major organ involvement (renal, neurological)	Common	Rare
Cutaneous findings	>75% (malar, discoid rash, oral ulcers)	~25% (purpura, erythema nodosum, SCLE)
Anti-dsDNA (%)	50–70	<5
Anti-ssDNA	Uncommon	Common (50% cases)
Antihistone antibodies (%)	50	>95
C3/C4 levels	Decreased	Normal
Antinuclear antibodies (%)	>95 (homogeneous, speckled; complement fixing)	>95 (always homogeneous; not complement fixing)
Anti-Sm antibodies (%)	30–40	Rare

SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

with strongly positive antibody to Smith/dsDNA would unequivocally have SLE, as in our case. Though quite uncommon, this paradox of positive anti-dsDNA and negative ANA has been reported in previous studies.[10] ANA can be detected by enzyme linked immunoassay or immunofluorescence assay; the latter is the 'gold standard'. In older studies, the incidence of ANA-negative SLE was estimated to be 5%.[11] However, it decreased to <2% when a Hep2 cell line was used as a routine substrate in an immunofluorescence assay.[10] ANA can be negative in the early phase of the disease, but about 10% of these patients may eventually become ANA positive.[11] However, treatment with immunosuppressive drugs may falsely keep these patients in a negative ANA state. Further, the ANA titre can be negative in patients with persistent profound proteinuria, entrapment of ANA in circulating immune complexes, antibody absorbed by tissue or for reason of technical inaccuracy. ANA-negative patients with SLE are known to have a higher prevalence of anti-Ro antibody and cutaneous manifestations. They have a lower prevalence of both central nervous system and renal involvement.

Learning points

- Tubercular infections in patients with systemic lupus erythematosus (SLE) are one of the most difficult conditions to manage as the diagnosis and treatment are difficult.
- A negative antinuclear antibody status does not rule out SLE; it more important to examine the clinical presentation and other specific blood tests.
- Drug-induced lupus erythematosus should be considered only for drug exposure of at least 1 month before lupus-like symptoms.

Competing interests None

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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