Overlap Syndrome with Rowell’s Syndrome, Antiphospholipid Syndrome, Primary Sterility, and Sensorineural Hearing Loss: A Case Report, Brief Review, and Analysis of Cases of Rowell’s Syndrome Reported from India and Abroad

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Abstract
Rowell’s syndrome (RS) is recognized since 1963 as a presentation of lupus erythematosus (LE) with erythema multiforme-like lesions and characteristic immunological changes. Antiphospholipid syndrome (APS) encompasses antibodies to phospholipids/phospholipid-binding cofactor proteins and/or circulating lupus anticoagulant with clinical manifestations of thrombosis such as recurrent spontaneous abortions, etc. A 32-year-old female with primary infertility since marriage (7 years) and sequential appearance, for the past 6 months, of various lupus-specific cutaneous lesions, “targetoid” lesions on palms, musculoskeletal, ocular and auditory (sensorineural hearing loss [SNHL]) complaints with positive serological profile for SMD-1, SS-A/Ro, SS-B/La, U1-snRNP, Ku, antiphospholipid and anticoagulant antibodies, and histopathologically confirmed LE is presented as a case of concurrent overlap syndrome, RS and APS, primary infertility, and SNHL. A brief review of RS including analysis of data of cases reported from India hereto vis-a-vis that of cases worldwide up to 2012 has also been done.

Key Words: Antiphospholipid syndrome, infertility, rowell’s syndrome, sensorineural hearing loss

Introduction
The rare entity of Rowell’s syndrome (RS) describes lupus erythematosus (LE), erythema multiforme (EM) like lesions, speckled antinuclear antibodies (ANA) with any to all of antiRo/La antibodies, rheumatoid factor, and chilblain. Anti-phospholipid syndrome (APS) entails thromboses, pregnancy complications such as recurrent fetal loss, preterm delivery, placental insufficiency and antibodies to phospholipids, cardiolipin, β2 glycoprotein, etc. We report the concurrence of these two syndromes with the sensorineural hearing loss (SNHL) and primary infertility. A brief review of RS and analysis of data of all reported cases from India hereto vis-a-vis that of cases worldwide has also been attempted.

Case Report
A 32-year-old housewife, unable to conceive for 7 years of marriage despite twice attempted in vitro fertilization and four cycles of oral clomiphene citrate and dydrogesterone tablets, presented with raised patches and plaques, some of the latter with cicatricial alopecia, over the scalp for 6 months. During the preceding month similar lesions in a photosensitive distribution, particularly itchy on exposure to sun, had appeared on her trunk and limbs. Simultaneously, occurrence of painful intraoral (buccal mucosa, palate/tongue) ulcers, swelling of both hands, arthralgia/myalgia and listlessness, ocular (watering, burning, and reddening) complaints, and loss of hearing made her seek dermatological consultation.

General physical examination revealed pallor. Systemic examination was normal. Dermatological examination [Figure 1a-f] revealed over scalp...
few (~10) dyspigmented macules and discoid plaques; the largest -3 cm×3 cm - over occiput with central atrophy, follicular plugging/accentuation, and scarring alopecia. Multiple dusky scaly macules/plaques were present in a photosensitive distribution over face, upper trunk, and upper limbs. “Targetoid” lesions – somewhat “faded” – were seen over the palms; said to be present since a fortnight. Metacarpophalangeal and proximal interphalangeal joints were tender. Hair was dry, brittle, and lusterless (lupus hair) over frontoparietal margins. Oral mucosa (buccal, hard palate, tongue, and lips) had multiple dyspigmented, at places, fissured patches.

Laboratory investigations revealed hemoglobin, 8.3 g/dL; white blood cell, 3400/mm³; erythrocyte sedimentation rate, 39 mm/1st h; rheumatoid factor, positive; ANA, 133U/ml; ANA blot, speckled on immunofluorescence, positive for SMD-1, SS-A/Ro, SS-B/La, U1-sn RNP; and Ku; antiphospholipid and anticardiolipin antibodies were positive. Pure-tone audiometry confirmed sensorineural deafness.

Table 1: Evolution of diagnostic criteria of Rowell’s syndrome

| Rowell et al.[1] (1963) | Lee et al.[1] (1995) | Zeitouni et al.[1] (2000) | Torchia et al.[4] (2012) |
|------------------------|---------------------|--------------------------|-------------------------|
| DLE with “EM-like” lesions | LE with “EM-like” lesions | Major criteria | Major criteria |
| Speckled ANA Anti-Sj-T Rheumatoid factor +ve | Speckled ANA Anti-La/SSB | LE (acute, subacute or discoid) EM-like lesions Speckled ANA | EM-like lesions At least one positive among these (speckled ANA, antiRo, antiLa) |
| | Rheumatoid factor +ve | Minor criteria | Negative DIF on lesional EM-like lesions Minor criteria |
| | | Chilblain Anti-Ro/anti-La Rheumatoid factor +ve | No triggering factors (medications or infection) |
| | | | Lack of EM lesions on acral or mucosal surfaces |
| | | | One other diagnostic criteria for SLE excluding discoid or malar rash, ANA, photosensitivity, oral ulcers or chilblains |

Diagnosis: All criterias Diagnosis: All criterias Diagnosis: All major+one minor criteria Diagnosis: All major+one minor criteria

Anti-Sj: Antibodies to saline extracts of human tissue, ANA: Antinuclear antibodies, DLE: Discoid lupus erythematosus, DIF: Direct immunofluorescence, EM: Erythema multiforme, LE: Lupus erythematosus, SLE: Systemic lupus erythematosus

Figure 1: (a) Hyperpigmented macules and patches over the face and ulceration over the lips. (b) Discoid plaque over the scalp with follicular accentuation and central atrophy. (c-e) Hyperpigmented plaques and patches over décolletage and upper limbs. (f) Targetoid lesions over the palms

Figure 2: (a) Follicular plugging, effaced rete ridges and mononuclear inflammatory infiltrate near the dermal-epidermal junction (H and E, ×100). (b) Lymphocytic infiltrate around the eccrine glands in the reticular dermis (H and E, ×400). (c) Interstitial mucin deposition (H and E, ×400)
### Table 2: Cases of Rowell’s syndrome reported from India

| Study                      | Case         | Type         | ANA     | RF | Other antibodies                  | Chilblain | Systemic Involvement | Duration | Inciting factor | Mucosal involvement |
|----------------------------|--------------|--------------|---------|----|------------------------------------|-----------|----------------------|----------|-----------------|---------------------|
| Khatri et al., 2000        | 22 year/female | SLE          | ND      | +  | -                                  | Yes       | +                   | 1 year   | None            | Sun                 |
| Dogra et al., 2000         | 65 year/female | SLE          | ND      | +  | -                                  | No        | +                   | 5 years  | None            | None                |
| Pandhi et al., 2003        | 23 year/female | SLE          | Speckled (1: 160) | +  | Anti RNP                          | No        | +                   | 5 months | None            | Sun                 |
| Khandpur et al., 2004      | 25 year/female | SLE          | Speckled (1: 80) | +  | Anti dsDNA                         | No        | +                   | 2 years  | None            | None                |
|                            | 29 year/female | SLE          | Speckled and Homogeneous (1: 80) | +  | Anti dsDNA                          | No        | +                   | 1 year   | None            | None                |
| Solanki LS et al., 2012    | 13 year/female | SLE          | Speckled (1: 160) | +  |                                  | No        | _                   | 6 months | None            | Sun                 |
| Solanki et al., 2014       | 11 year/female | SCLE         | (1:80) ND | +  | Anti dsDNA                         | No        | _                   | 2 weeks  | None            | _                   |
| Santhanam et al., 2014     | 11 year/female | SLE          | Speckled | -  | Anti-Ro                            | No        | _                   | _        | _              | _                   |
| Bhat et al., 2014          | 15 year/male  | SLE lupus nephritis | Speckled | +  | Anti dsDNA + Anti Ro + Anti La + Anti-nucleosome + Anti-histone + Anti-dsDNA | Yes       | _                   | 3 years  | None            | _                   |
| Lahiri et al., 2015        | 20 year/female | SLE          | Speckled | +  | Anti dsDNA + Anti Ro + Anti La     | Yes       | +                   | 1 year   | None            | _                   |
| Bhobe et al., 2015         | 18 year/female | SLE lupus nephritis | Speckled (1: 160) | -  | Anti-Ro                            | No        | _                   | 1 month  | None            | _                   |
| Madke and Khopkar 2015     | 33 year/male  | DLE          | Speckled | -  | Anti dsDNA + Anti Ro + Anti La     | No        | +                   | 4 months | None            | Sun                 |
|                            |              |              |         |    |                                     |           |                      |          |                 |                     |

Contd...
| Study                              | Case          | Type               | ANA        | RF          | Other antibodies                     | Chilblain | Systemic Involvement | Duration | Inciting factor | Mucosal involvement |
|-----------------------------------|---------------|--------------------|------------|-------------|--------------------------------------|-----------|----------------------|----------|-----------------|---------------------|
| Kaur and Sharma 2016[1]           | 25 year/female| SLE                | Negative   | +           | +Anti Ro                             | Yes       | -                    | -         | 7 months        | None                |
| Anjay and Hemachandar 2016[6]     | 20 year/female| SLE lupus nephritis| Speckled   | +           | +Anti- dsDNA                          | No        | +                   | +         | 2 weeks         | None                |
| Siddhavatam et al., 2017[1]      | 23 year/female| SLE Sjogren syndrome| Speckled   | (1: 160)    | +Anti-SMC1                           | No        | +                   |          | 3 months        | None                |
| Sharma and Sharma 2017[12]       | 38 year/female| SLE                | Speckled   | (1:640)     | +anti- dsDNA +anti Ro                | Yes       | +                   |          | 1 month         | None                |
| Singh et al., 2017[13]           | 30 year/male  | SLE lupus nephritis| Speckled   |             | +Anti- dsDNA +anti La                | Yes       | +                   |          | 2 months        | None                |
| Present case                      | 32 years/female| SLE                | Speckled   |             | +Anti-SMD-1+Anti-SS-A/Ro +Anti-SS-B/La +AntiU1-snRNP +Anti- Ku | No        | +                   |          | 6 months        | None                |
|                                   |               | Antiphospholipid syndrome|             |             |                                      |           |                      |          |                 | Oral, buccal mucosa, palate |

ANA: Antinuclear antibody, DLE: Discoid lupus erythematosus, RF: Rheumatoid factor, SCLE: Subacute cutaneous lupus erythematosus, SLE: Systemic lupus erythematosus, ND: Not done
Table 3: Analysis of Indian vis-à-vis worldwide cases of Rowell’s syndrome

| Indian studies (n=18) | Worldwide literature (n=95) |
|-----------------------|-----------------------------|
| Age                   |                             |
| 11-65 (median, 23)    | 9-87 (median, 32)           |
| Gender (female:male)  |                             |
| 5:1                   | 8.1:1                       |
| LE-specific mucocutaneous (%) |                |
| SLE                   | 88.88                       |
| SCLE                  | 5.56                        |
| DLE                   | 5.56                        |
| Systemic involvement (%) |                         |
| Hematological         | 66.67                       |
| Renal                 | 22.22                       |

SCLE: Subacute cutaneous lupus erythematosus, SLE: Systemic lupus erythematosus, DLE: Discoid lupus erythematosus

Histopathological examination of the scalp lesion was opined as discoid LE [Figure 2a-c]. Overlap syndrome with Rowell’s and antiphospholipid antibody syndromes, primary infertility, and SNHL was the likely diagnoses given to the above clinical, histopathological, and serological findings, though the latter lacked direct immunofluorescence study of the targetoid lesions due to unaffordability. Administration of daily oral prednisolone (20 mg), hydroxychloroquine (200 mg), along with application of mometasone furoate (0.1%) ointment and broad-spectrum sunscreen led to significant relief within a fortnight. She was discharged on request, giving a written referral to the specialist in reproductive medicine and advised follow-up with us and the rheumatologist. However, for want of follow-up by the patient, confirmation of APS by repeat testing of antiphospholipid and anticardiolipin antibodies could not be carried out.

Discussion and a Brief Review

Bhobe et al. stated that Scholtz first reported in 1922 a case of LE with EM. The diagnostic criteria [Table 1] initially proposed in 1963 by Rowell et al. – for a syndrome (considered the first in the connective tissue disorders and later eponymously designated after Rowell) in four adult female cases from among their 120 discoid LE patients have been subsequently amended thrice. Even the existence of RS as criteria for the disease was questioned; some considering the association to be merely coincidental; others, a form of subacute cutaneous LE and still others – LE associated Steven–Johnson syndrome/toxic epidermal necrolysis.

Heretofore seventeen cases of RS have been reported from India [Table 2], ours being the eighteenth. Salient findings on an analysis of data of these eighteen cases from India vis-a-vis that of the 95 cases reported worldwide until 2012 are presented in Table 3. Earlier Khandpur et al. had reported two cases of RS and compared their findings with those of the eighteen cases of this syndrome up to 2000 worldwide.

Unlike Madke et al. who proposed only Ro/La antibodies as a criterion (minor), our analysis of the cases of RS from India revealed the most common ANA (10; 55.56%) to be anti-dsDNA with concurrent lupus nephritis in three (16.67%).

Fourteen (77.78%) of the Indian cases had speckled pattern ANA; one negative for ANA had Ro/La antibodies. The immunoflourescence pattern was not done in the remaining three who had raised ANA titers. Rheumatoid factor was positive in 12 (66.67%) of the Indian patients. The involvement of systems in the Indian cases was more common than that in the reappraised worldwide cases [Table 3].

APS is defined by the presence (twice with a minimal interval of 6 weeks) of antiphospholipid antibodies and associated phospholipid-binding cofactor proteins and/or a circulating lupus anticoagulant together with clinical manifestations such as thrombosis, recurrent spontaneous abortions, etc.

McCabe, in 1979, first reported rapidly progressing bilateral SNHL in this syndrome and postulated autoimmunity to be potentially pathogenetic, best understood by analyzing the nature of the thrombotic process over its time course and size of the involved vessels. Thrombosis could result from thrombotic microangiopathy or ischemia — initiated primarily by activated endothelial cells or secondarily by induced free radicals. Isolated inner ear disease might involve small vessels of the labyrinthine circulation.

Binding of the antiphospholipid antibodies to β2 glycoprotein is not only well established as a cause of fetal loss but also has the potential to cause faulty implantation, placentation and even early embryonic development by breaking down the phospholipid adhesion molecules between different elements of trophoblast. Lupus anticoagulant and anticardiolipin antibodies have also been implicated in the prothrombotic effects of APS.

Conclusion

Our case – ostensibly the eighteenth of RS from India and the first reporting its concurrence with APS, primary infertility and SNHL with overlap syndrome — who initially presented for management of infertility to the concerned specialist, continued to suffer from ongoing stress as the possibility of APS got overlooked. Not only...
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did infertility and SNHL continue to progress, overlap syndrome and RS also got precipitated. Hopefully, this report reiterated the need for heightening the index of suspicion of this rare association.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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