functionally distinct subunits: H-ferritin and L-ferritin [9]. H-ferritin plays the major role in the rapid detoxification of iron and intracellular iron transport, whereas L-ferritin is involved in iron nucleation, mineralization and long-term storage. The expression of ferritin is regulated at both the transcriptional and post-transcriptional levels by iron, hormones, cytokines, including IL-1α and TNF-α, and oxidative stress. Ferritin protects cells against damage due to oxidative stress [8–10]. In the present study, the high level of serum ferritin may be attributable to the intensity of the hypoxia and inflammation caused by systemic activated macrophages in patients with C-ADM-related RP-ILD.

In general, DAD is not always associated with significant macrophage presence. However, it has been reported that DAD with a pronounced increase in macrophages was seen in the alveoli and the interstitium of the lung in severe acute respiratory syndrome (SARS) and that direct injury of virus on alveolar epithelium, prominent macrophage infiltration and distinctive fibroblast proliferation may play major roles in the pathogenesis of SARS. We speculated that increasing alveolar macrophages could be found specifically in some kind of DAD, such as SARS and C-ADM-related RP-ILD. We hypothesized that the regulation of activated macrophages may represent a potent therapy for C-ADM-related RP-ILD.

Rheumatology key message
• A high level of serum ferritin is attributable to systemic activated macrophages in C-ADM-related RP-ILD.

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B-cell chronic lymphocytic leukaemia presenting as lower motor neuron disease and SS

Sir, We present the case of a 57-year-old female patient with B-cell chronic lymphocytic leukaemia (CLL) presenting as lower motor neuron disease (LMND) and SS. In May 2009, an LMND diagnosis was established on the basis of asymmetrical muscle weakness of upper and lower extremities, muscle atrophy and diffuse fasciculation. Additionally, the patient’s EMG and nerve conduction studies in the upper extremities and thoracic region showed signs of denervation without motor conduction block. Muscle biopsy of the right branchial bicep revealed perivascular and perimysial inflammation by lymphocytes and plasma cells (Fig. 1a). Two months later, SS was diagnosed according to the presence of sicca symptoms, anti-Ro (SS-A) positivity and salivary gland biopsy focus score (Grade 3 Tarpley classification) (Fig. 1b). Five months post-SS diagnosis, during routine follow-up, mild hepatosplenomegaly and neutropenia were noted. Bone marrow biopsy revealed interstitial lymphocytic
infiltration of small B lymphocytes (30%). Immunophenotyping demonstrated a monoclonal B-cell population expressing CD5, CD23, CD38, CD43 and HLA-DR and weak expression of CD20, CD79b and FMC7, findings compatible with CLL. Analysis of immunoglobulin VH gene segments revealed a mutated VH3-30*03 immunoglobulin antigen receptor. Retrospective immunohistochemistry studies of the muscle and salivary gland biopsies revealed infiltration of monoclonal B cells expressing CD20, CD5, CD43 and CD23 markers. Sural nerve biopsy did not reveal lymphocytic infiltration. After 4-weekly pulses with rituximab, the patient displayed a significant improvement in both muscle strength and sicca symptoms.

Typical CLL is often found incidentally, on a routine laboratory evaluation. Common manifestations of the disease include fatigue, autoimmune haemolytic anaemia, frequent infections, splenomegaly, hepatomegaly, lymphadenopathy or extranodal infiltrations. Autoimmune complications occur in up to a quarter of CLL patients and predominantly target blood cells [1]. Clinical syndromes mimicking RA, SLE and SS in the course of CLL have also been described. Duk et al. [2] described a study population of 964 CLL patients, from which 115 were found to have autoimmune disorders. SS was documented in only three of the 115 CLL patients. It is well documented that patients affected by lymphoproliferative disease (LPD), including CLL, can develop MND, but the frequency has yet to be established. Although some authors suggest that LPD is disproportionately frequent in MND patients compared with the general population, this association could be coincidental [3].

Studies have established that CLL cells can produce mAbs that bind autoantigens in a polyreactive manner [4]. Furthermore, it has been suggested that all CLL cells are likely derived from autoreactive B-cell clones, the polyreactivity of which depends on the presence or not of somatic hypermutation process. Interestingly, CLL B cells express a distinct and restricted antibody repertoire, which also suggests a selection process driven by specific antigens supporting the concept that all CLL cells are antigen experienced. Recombinant CLL-derived mAbs react with autoantibodies associated with cellular apoptosis suggesting that clonal expansion in CLL may be stimulated by autoantigens occurring naturally during apoptosis [5]. Through apoptosis and exosome formation, salivary epithelial cells in SS patients present intracellular autoantigens contributing to tolerance breakdown [6]. Consequently, it would seem safe to assume that the deregulated salivary epithelium of SS could result in uncontrolled antigenic stimulation of CLL B-cell clones. Although, it is unclear whether in our case the translocated autoantigen SS-A to the apoptotic blebs is responsible for the expansion of the CLL clone, this mechanism is the most probable to explain in our patient the coexistence of CLL and SS.

The concomitant diagnosis of LMND increased the complexity of this case. Neuroinflammation is a characteristic of pathologically affected tissue in LMND. They include an accumulation of large numbers of activated microglia and astrocytes, as well as small numbers of T cells, mostly adhering to post-capillary venules. There is increasing evidence that a disproportionate number of patients with LMND have a coexisting lymphoproliferative disorder or monoclonal gammopathy [3]. It has been suggested that lymphoma cells may produce autoantibodies that bind to abnormally glycosylated spinal motor neurons resulting in neuronal dysfunction [7]. This does not seem to apply in our case since, despite the presence of CLL lymphocytic infiltration in the muscle biopsy, the sural nerve was free of findings.

Both SS and LMND have been documented in the course of CLL but, to our knowledge, concomitant occurrence of these three clinical entities has not been reported. This case illustrates the implication of CLL cells in the initiation and perpetuation of autoimmunity as well as the potential capacity of the disease to invade extranodal sites, creating unusual clinical manifestations that pose a diagnostic challenge for clinicians.

Rheumatology key message

- Extranodal CLL manifestations always present a diagnostic dilemma.

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SIR, The lack of specificity of the new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for classification of RA [1] may have suffered its first casualty [2]. Periarticular osteopenia has classically been considered part of RA [3, 4]. Alves et al. [2] were unable to distinguish any difference in periarticular bone density using dual-energy X-ray absorptiometry (DEXA) averaging of three and four MCP joints of the most affected hand. There appears to be four possible explanations:

(i) There is no significantly increased occurrence of periarticular osteopenia in RA. This is contrary to observations in definitively diagnosed RA [5].

(ii) Given the study entry criteria of one swollen joint or pain or loss of motion in at least two joints, there may have been limited MCP joint involvement. If periarticular osteopenia has any relationship to inflammation, the normal density of unaffected joints may have camouflaged the periarticular osteopenia in an afflicted joint. This could simply represent an averaging artefact.

(iii) DEXA averaging of three or four joint groups may not have the spatial resolution afforded by examination of standard X-rays. Localization of DEXA regions of interest (ROIs) variably includes diaphyseal bone adjacent to the peri-articular region [2]. This again could simply represent an averaging artefact.

(iv) Lack of specificity of ACR/EULAR criteria may be responsible [1], as other forms of polyarthritis (e.g. SpA) do not appear excluded. Even before proposal of these new criteria, there has been controversy as to which criteria are appropriate [6], with some lumping polyarticular inflammatory arthritis whereas others split off those who have subchondral (rather than solely marginal) erosions. The archeological record [7] and biomechanical engineering studies [8, 9] support the splitters, as the split-off group has characteristics indistinguishable from other individuals diagnosed with SpA [6]. Fifty per cent of the split-off and SpA groups do not manifest periarticular osteopenia and may actually have new bone formation (increased density).

All four possibilities should be considered. If possibilities (ii) and (iii) explain the findings, then DEXA would appear to have no role in addressing the question of periarticular osteopenia. If the first possibility explained the observations by Alves et al. [2], there may have been no reason to even perform the study. However, the most likely explanation may be the lack of specificity of entry criteria. The ACR/EULAR certainly are most helpful for making the diagnosis of RA that many insurance companies (at least in the USA) require for prescription of biologic agents. This solves the physician’s patient care dilemma, as uSpA has not been one of the insurance company criteria for allowing such therapy. However, lumping disparate diseases may be compromising our ability to understand their nature.

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