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Case Report

A unique case of extranodal marginal zone lymphoma with synchronous pulmonary and dermatologic manifestations

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ABSTRACT

An 89-year-old male with a medical history of non-ischemic cardiomyopathy was initially admitted with acute hypoxic respiratory failure attributed to heart failure exacerbation. Aside from progressive dyspnea, a non-pruritic, non-painful rash and constitutional symptoms were reported. Initial work-up was remarkable for normocytic anemia, lymphopenia, mild hypercalcemia, and elevated inflammatory markers. Despite aggressive diuresis, his respiratory distress worsened requiring up-titration of supplemental oxygen (6–8L/min). Subsequent chest CT showed diffuse, ill-defined areas of consolidation and ground-glass opacities (GGOs) with areas of solid and ground-glass nodularity. Rheumatologic work-up was remarkable for mildly elevated ANA titer of 1:60, and positive anti-centromere antibody of 1.8 AI (normal range 0–0.9 AI). Infectious work-up was negative. Due to high oxygen requirements, tissue sampling was obtained by skin biopsy instead of bronchoscopy. After biopsy testing, prednisone 60 mg was started with posterior clinical and radiographic improvement. Biopsy results revealed cutaneous MZL. Follow-up PET scan showed persistent but improved diffuse GGOs and nodular opacities. Given the clinical presentation, imaging and skin biopsy results, the diagnosis was compatible with EMZL with synchronous pulmonary and skin manifestations. Empiric treatment with Rituximab and steroid taper was planned. At 6-month follow-up, the patient reported clinical and respiratory improvement.

1. Background

Extranodal marginal zone lymphoma (EMZL) is a heterogeneous disease with a variable clinical presentation, typically associated with the tissue involved. EMZL accounts for 61 % of marginal zone lymphomas (MZL) with pulmonary marginal zone lymphoma (PMZL) being 9–14 % of these. Respiratory symptoms are usually present at the time of diagnosis of PMZL and diverse patterns of lung abnormalities can be observed on imaging studies. Biopsy of the affected site remains the gold-standard for diagnosis of EMZL, and morphological, flow-cytometry, and genetic analysis are recommended. However, there are instances in which involvement of other surfaces is noted, and biopsy of these might be enough for diagnostic purposes. To our knowledge, there are only a handful of cases in the literature reporting EMZL with synchronous pulmonary and skin involvement. We present a case of an 89-year-old patient who developed acute hypoxic respiratory failure from presumptive heart failure exacerbation, later found to have EMZL with synchronous pulmonary and skin involvement ultimately diagnosed via skin biopsy.

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2. Case presentation

An 89-year-old male with a past medical history significant for non-ischemic cardiomyopathy (with a left ventricular ejection fraction of 50 % on most recent transthoracic echocardiogram), atrial fibrillation, and hypertension who was initially admitted with acute hypoxic respiratory failure attributed to heart failure exacerbation. Aside from the severe dyspnea on minimal exertion that brought him to the hospital, the patient reported a 6-week history of progressive, non-pruritic, non-painful chest and left arm rash (Fig. 1) as well as a 15-pound weight loss 6-months prior presentation. He denied any recent symptoms of aspiration, respiratory infections, toxin and/or chemical exposures. Upon arrival, he was started on aggressive diuresis and broad-spectrum antibiotics given concern for underlying pulmonary infection as a culprit of his decompensated heart failure.

24-h after admission, despite aggressive diuresis, the patient developed worsening respiratory distress needing up to 6–8L of supplemental oxygen via nasal cannula. Computed Tomography (CT) of the chest was obtained and showed diffuse ill-defined areas of consolidation and ground-glass opacities with additional areas of solid and ground-glass nodularities (Fig. 2). Initial work up was remarkable for a normocytic anemia with a hemoglobin of 10.7 g/dL (normal range 13.7–17.5 g/dL) and hematocrit of 33 % (normal range 40–51 %), lymphopenia of 0.4 THOU/uL (normal range 1.3–3.6 THOU/uL) on complete blood count. Mild hypercalcemia 10.8 mg/dL (normal 8.6–10.2 mg/dL) on basic metabolic panel. Elevated inflammatory markers with a CRP of 26 mg/L (normal range 0–8 mg/L) and ESR of 43 mm/hr (normal 0–20 mm/hr). Based on his clinical presentation and lack of improvement with initial treatment, the differential diagnosis was broadened to include granulomatosis with polyangiitis, sarcoidosis, and possible underlying malignancy with pulmonary manifestations. Rheumatologic work-up was notable for positive ANA screen with anticentromere pattern and titer of 1:60, positive Anti-Centromere Antibody positive 1.8 AI (normal range 0–0.9 AI), indeterminate ANCA but negative MPO and PR3 antibodies. Broad infectious work-up with unrevealing blood cultures, HIV, hepatitis panel, urine Streptococcus pneumonia and Legionella antigens, MRSA nasal swab, Cryptococcus cultures and Mycoplasma nucleic acid amplification test. A broncho alveolar lavage was not performed due to escalating oxygen requirements.

Given our high level of suspicion for the skin findings being associated to the pulmonary findings and overall clinical presentation, a skin biopsy was performed to help with diagnostic purposes. In addition, given the patient's persistent hypoxic respiratory failure despite current management, the patient was started on prednisone 60 mg (1mg/kg/day) with rapid clinical and radiographic improvement (Fig. 3A). A prolonged steroid taper was planned with Rheumatology and Pulmonology out-patient follow-up. The final skin biopsy result came back positive for cutaneous marginal zone lymphoma. Oncology referral was arranged and a PET scan was recommended which showed decrease in size of multiple hypermetabolic mediastinal lymph nodes and persistent but improved diffuse airspace disease consisting of patchy ill-defined hypermetabolic ground glass and nodular opacities predominantly throughout the perihilar regions (Fig. 3B). Given clinical presentation, PET scan findings and final biopsy results, extranodal marginal zone lymphoma with synchronous pulmonary and skin manifestations was the most likely unifying diagnosis, thus empiric treatment with Rituximab and prolonged steroid taper was recommended. During his six-month follow-up in Pulmonology clinic, the patient reported improved energy levels, ambulation, improved appetite, and no supplemental oxygen requirements. While his oncologic disease remained stable, his heart failure continued to progress and eventually the patient passed away from ongoing comorbidities.

3. Discussion

EMZL, also called mucosa-associated lymphoid tissue (MALT) lymphoma, is a low-grade B cell non-Hodgkin lymphoma. It is clinically indolent and postulated to arise from the B lymphocytes of the marginal zone, which is the external part of the secondary

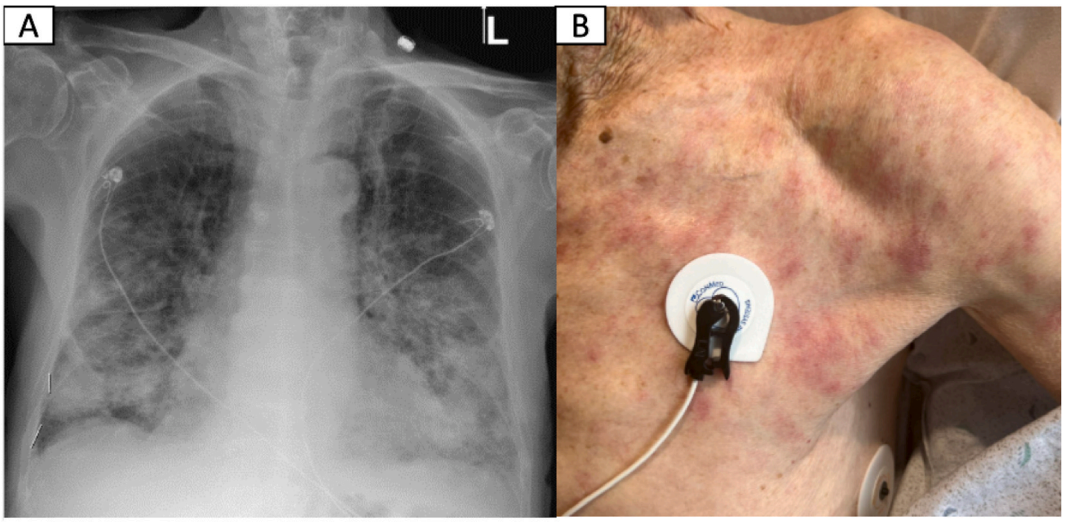

Fig. 1. A: Chest X-ray on admission. B: Subacute rash in chest and arms.

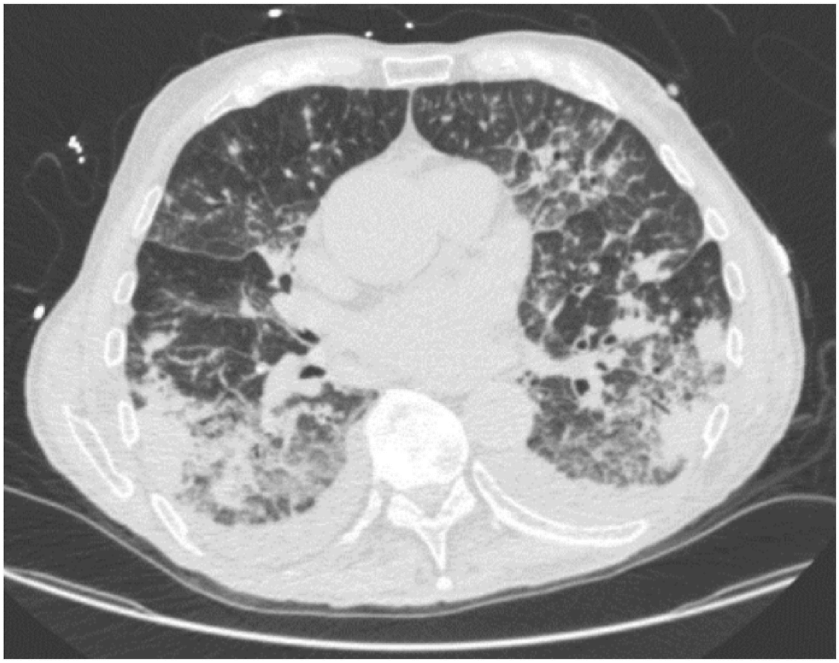

Fig. 2. CT chest with multiple ground glass opacities, with solild and ground glass nodularity.

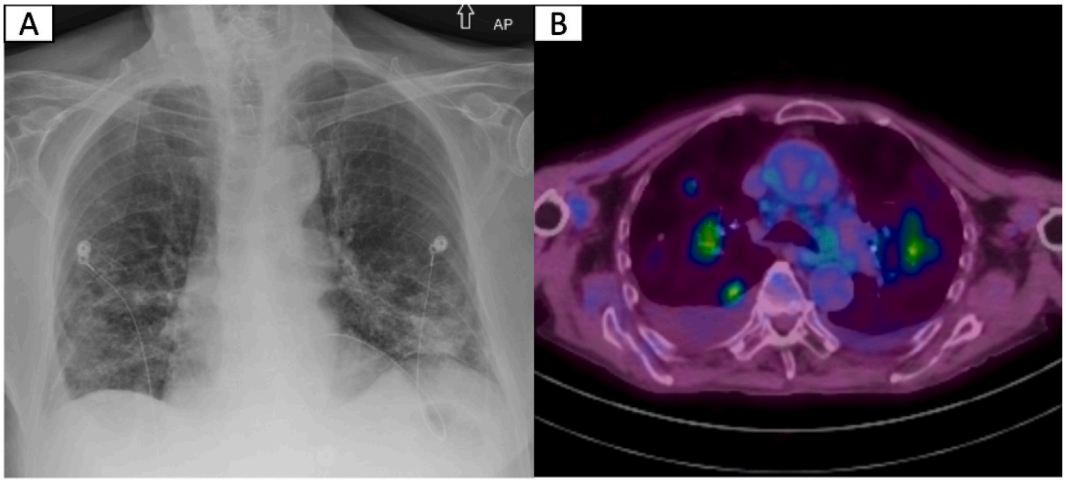

Fig. 3. A: Chest X-ray upon discharge with radiographic improvement. B: PET scan with persistent hypermetabolic ground glass opacities and hilar lymphadenopathy.

lymphoid follicles [1]. EMZL accounts for approximately 61 % of marginal zone lymphomas (MZL) with pulmonary and cutaneous marginal zone lymphomas comprising approximately 9%–14 % and 10 % of these, respectively [2,3]. EMZL is often caused by chronic antigenic stimulation by infectious pathogens (eg H. pylori, hep C virus, HIV and others) or autoimmunity (particularly Sjogren's syndrome and Hashimoto Disease) leading to inflammatory lymphoid populations which can arise in widely varied sites [1,2,3]. By the same mechanism, PMZL arises from bronchus-associated lymphoma tissue (BALT), which is a component of the pulmonary lymphoid system [3].

The clinical presentation of EMZL varies significantly with tissue involvement. In PMZL, the clinical presentation varies from asymptomatic (nearly half of the patients) to nonspecific symptoms such as cough, dyspnea, chest pain with an unrevealing physical examination. Constitutional symptoms such as fever and weight loss are present in less than 25 % of the patients and are associated with aggressive disease [3]. Similarly, patients with cutaneous MALT lymphoma typically present with poorly defined erythematous patches/plaques typically on the head and neck area, to more superficial papules exclusively involving the upper trunk, extremities, or both [4]. Our patient presented with a constellation of symptoms involving both organs with progressive dyspnea on exertion,

constitutional symptoms, and skin lesions distributed throughout the chest and arms raising our suspicion for underlying malignancy rather than infectious etiologies.

Multiorgan MALT lymphomas have been hardly reported as EMZL usually remains localized to the tissue of origin for a prolonged period of time. Raderer et al. found that extra-gastrointestinal MALT lymphomas disseminate more often than gastrointestinal MALT lymphoma, making the gastrointestinal tract the most common site for dissemination [5]. Similarly, a case series of multiorgan MALT lymphoma reported the appearance of secondary organ involvement usually happened months after the initial diagnosis [6]. The uniqueness of our case resides in the presence of synchronous pulmonary and skin involvement of EMZL which has not been reported to our knowledge.

Biopsy of the affected site is the gold-standard for diagnosis of EMZL. Additional testing such as morphological, flow-cytometry, and genetic analysis are recommended. The morphology typically reproduces the normal mucosa-associated lymphoid tissue with reactive follicles occupying the marginal zone. On immunophenotypic analysis, the cells are positive for B-cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and CD23 [1,2,4,7–10]. On CT scans, PMZL usually manifests with bilateral (60–70 %) and multiple (70–77 %) lesions in a random distribution. The most frequent lesions reported are lobar or segmental consolidations (60–65 %), followed by nodules (45–55 %) and masses (21–44 %) [8,9,11]. Furthermore, other patterns reported were ground glass opacities (GGOs) in 6–41 %, pleural effusions in 21 %, cavitary lesions and lymphangitic spread in 9 % of imaging studies [9].

Several approaches may be required to obtain sufficient information for a correct diagnosis. Invasive procedures like bronchial and transbronchial biopsies are more fruitful when carried out on endobronchial lesions or guided by the topography of abnormalities. However, the presence of endobronchial lesions is extremely rare, and bronchoscopic evaluation is usually normal [3]. Similarly, BAL with the presence of lymphocytic alveolitis can be indicative of primary pulmonary lymphoma, albeit these findings are not specific and additional testing may be required. In our particular case, studies like CT-guided aspiration and biopsy could have been also considered for diagnosis. However, presence of skin lesions and risk-benefit analysis due to age, high oxygen requirement and localization of the pulmonary lesions were taken into consideration to decide for a noninvasive and pragmatic approach with a skin biopsy. Positive skin biopsy in conjunction with findings in PET scan during steroids treatment suggested EMZL as unifying diagnosis.

Finally, treatment is usually stage-dependent. Patient with localized disease typically undergo local therapy, like radiation. Advanced disease is treated with systemic therapy like immunotherapy or chemoimmunotherapy. Systemic therapy, like in our patient, is usually reserved to patients in advanced disease or if radiation is not feasible. Rituximab, a CD20 monoclonal antibody, with good tolerability and response s in the 80 % range is typically the treatment of choice. (reference)

The originality of our case resides in the unique presentation of EMZL, involving lung and skin simultaneously, which to our knowledge, no other case has been reported in the literature. Biopsy of the affected site is the gold-standard for diagnosis of EMZL. In our approach, we exemplify a practical strategy by opting to sample tissue from the skin, the most accessible organ, as a means to establish the diagnosis. The synchronous presentation coupled with characteristic CT findings of PMZL validated our decision to diagnose with EMZL with multiorgan involvement. Prompt plan to treat EMZL is particularly important given the increased mortality in similar clinical scenarios.

CRediT authorship contribution statement

Carlo Arevalo: Conceptualization, Writing – original draft, Writing – review & editing. **Fernando Camacho:** Writing – original draft, Writing – review & editing. **Joseph Modrak:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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