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Case Report

The occurrence of sarcoidosis after treatment of nodal marginal B-cell zone lymphoma in a 56-year-old male: A case report from Syria

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ABSTRACT

Introduction: Sarcoidosis is a chronic systematic inflammatory disorder of unknown etiology. Marginal zone lymphoma is a well-varied family of lymphomas that makes up to 10% of the overall non-Hodgkin's lymphomas. The relationship between sarcoidosis and multiple diseases was mentioned repeatedly in the literature, whereas the relationship between sarcoidosis and marginal zone lymphoma was found rare. This case presents a 56-years-old man who was diagnosed with sarcoidosis after treatment of marginal zone lymphoma.

Case presentation: A 56-year-old male presented to Tishreen University Hospital (TUH) Gastrointestinal department with abdominal pain, vomiting, loss of apetite, fever, and unintentional weight loss. Computerized tomography scan of the chest and abdomen, in addition to the excisional biopsy of the cervical nodes, were both highly suggestive of marginal zone lymphoma. After completing a course of chemotherapy, the patient returned with generalized abdominal discomfort, anorexia, and fatigue. Computerized tomography illustrated enlarged mediastinal lymph nodes in the chest and the abdomen. Microscopic examination of an abdominal lymph node revealed granulomatous lymphadenitis with sarcoidosis. Thereafter, the patient was managed with nonsteroidal anti-inflammatory drugs and corticosteroids.

Conclusion: We describe the occurrence of sarcoidosis after the treatment of marginal zone lymphoma. In most cases, sarcoidosis precedes lymphomas. This case emphasizes the evidence on the possible relationship between lymphomas and sarcoidosis, and attention should be sought towards any new manifestations throughout the follow-up of patients diagnosed with lymphomas toward sarcoidosis as part of our differential diagnosis.

1. Introduction

Sarcoidosis is a chronic systematic inflammatory disorder of unknown etiology [1]. The most involved organs are the hilar lymph nodes, lungs, and mediastinal lymph nodes [2]. Marginal zone lymphoma (MZL) is a well-varied family of lymphomas that makes up to 10% of the overall Non-Hodgkin's lymphomas [3]. It is divided into three clinicopathological subtypes: splenic marginal zone lymphoma, extra-nodal marginal zone lymphoma, and nodal marginal zone lymphoma (NMZL) [3]. The relationship between sarcoidosis and marginal zone lymphoma was found rare in the literature. The published studies that presented the co-existence of the former two conditions included one of the following dural-based marginal zone lymphoma [4], marginal zone lymphoma of the esophagus [1], or pulmonary mucosa-associated lymphoid tissue lymphoma [5]. This case presents a 56-years-old white man who was diagnosed with sarcoidosis after the treatment of MZL.

2. Case presentation

A 56-year-old male presented to Tishreen University Hospital (TUH) Gastrointestinal department with abdominal pain, vomiting, loss of apetite, fever, and unintentional weight loss. Clinical examination showed a firm, swollen, non-motile lymph node in the left side of the neck with unclear boundaries, painful during palpation. The patient was a heavy smoker 50 pack per year for 30 years with unremarkable family and medical history, and the absence of any traumas or surgical interventions. no drugs or allergies were recorded. Posterior anterior chest x-ray showed manifestations of interstitial lung syndrome. The former imaging diagnostic revealed a massive air bubble in the superior lobe, in addition to densities located in the left basal and intermediate right

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lobes, which are consistent with atelectasis (Fig. 1). Abdominal echography showed large number of massive hypoechoic lymph nodes at the level of the hepatic umbilicus, renal umbilicus, and retroperitoneum in the epigastric region peri aorta (Fig. 2).

Computerized tomography (CT) scan of the chest and abdomen with contrast showed emphysema, especially in the superior sections of upper lobes, nodular hyperplasia in the middle third of the right pulmonary area, and around the abdominal aorta and in the celiac group. The largest one measures 32 mm in diameter (Fig. 3). Bone marrow biopsy was performed in Tishreen University Hospital (TUH) district Oncology and Hematology, on the hand of a junior trainee with 4 years of hematological training and after having the consent of the patient, which revealed hypercellularity for age up to 50% with trilineage hematopoiesis. Scattered mild reactive lymphoplasmacytic infiltrates and no evidence of malignancy.

An excisional biopsy of the cervical nodes was performed by a general surgery specialist in the general surgery department in TUH, after having the consent of the patient, which showed the diagnosis of marginal zone lymphoma with plasma cell differentiation. For typing and confirmation purposes, immune stains of the cervical lymph node demonstrated positivity for CD20 and Bcl2 in the marginal cells, CD138+ in the many plasma cells, whereas CD10 and CD3 were negative. Therefore, it was confirmed as marginal zone B-cells lymphoma (Figs. 4–6). The patient was treated with a four-cycles course of rituximab and bendamustine. After completing the course of chemotherapy, which was well explained to the patient, the patient showed a full recovery of MZL and returned to his daily routines and activities with no mentioned obstacles as expected. Doses and dates of each cycles are as following:

First cycle: September 18, 2019	
Second cycle: October 6, 2019	• Rituximab 700 mg
Third cycle: December 4, 2019	•Bundamistin 150 mg
Fourth cycle: January 15, 2019	

He also received during his stay in the hospital, in addition to chemotherapy, pain killer like Morphine 10 mg and Paracetamol1 g.

Two years later the patient had returned to Oncology department with generalized abdominal discomfort, anorexia, and fatigue. Physical examination showed abdominal tenderness. Due to the history of MZL, a

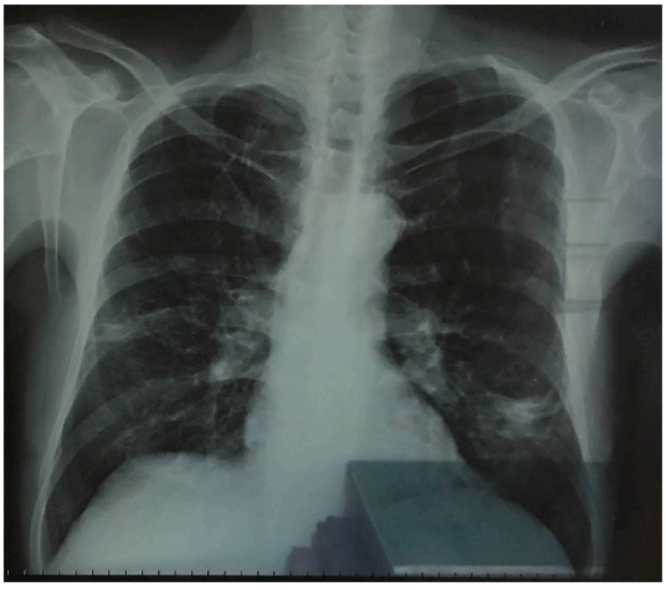

Fig. 1. Posterior anterior chest x-ray showed manifestations of interstitial lung syndrome. The former imaging diagnostic revealed a massive air bubble in the superior lobe, in addition to densities located in the left basal and intermediate right lobes, which are consistent with atelectasis.

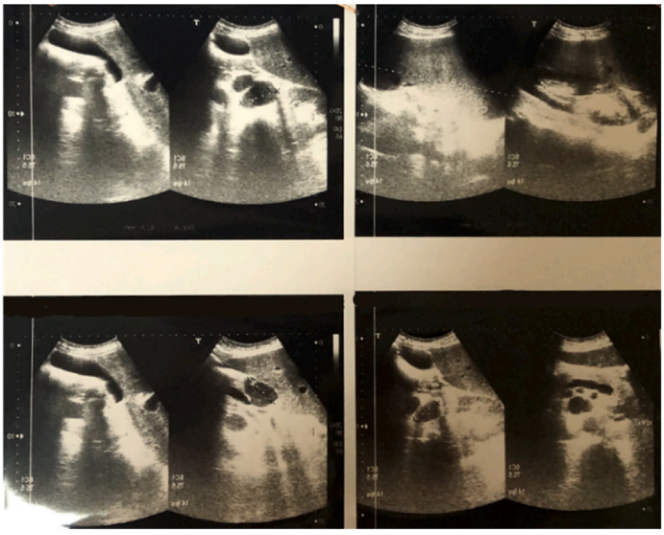

Fig. 2. Abdominal echography showed large number of massive hypoechoic lymph nodes at the level of the hepatic umbilicus, renal umbilicus, and retroperitoneum in the epigastric region peri aorta.

full-body CT scan was required and showed: Enlarged mediastinal lymph nodes around the trachea, the largest one was (2.2 cm) in diameter, a large lump under the carina measuring (4.5 × 2.5 cm), an enlarged lymph node in the left and right pulmonary navel measuring (1.3 × 2.6 cm) (1.9 × 2.3 cm) respectively, a large number of enlarged lymph nodes are observed around the ventricular aorta and retroperitoneum the largest one measures (3.7 × 3.8 cm). An excisional biopsy of an abdominal lymph node was performed, with (1,5 × 2 cm) in size, gray-tan in color, and soft to rubbery in inconsistency (Fig. 7). Microscopic examination revealed granulomatous lymphadenitis with sarcoidosis (Fig. 8). 18F-FDG-PET showed mediastinal lymphadenopathy with increased fluorodeoxyglucose uptake in the abdominal nodes (Fig. 9). The patient was managed with nonsteroidal anti-inflammatory drugs and corticosteroids without pursuing with any chemotherapy regimen.

During a checkup visit, a whole-body CT was performed and showed a gradual recovery as expected, as the tracheal node shrank into 1 cm, the right and left navel nodes measurements reached (14mm, 9 mm respectively). A significant bilateral reticular fibrosis was recognized with the appearance of honeycomb shape. Moreover, the largest aortic lymph node measured 3 cm (Fig. 10).

3. Discussion

Marginal zone lymphomas are type of indolent non-Hodgkin's lymphomas, which originates from B-cells of the marginal zone of the lymphoid follicles [6,7]. MZL comes in second place as the most frequent subtype of indolent B cell non-Hodgkin's lymphoma. NMZL is the least common subtype of marginal zone lymphoma and accounts for 1% of non-Hodgkin lymphomas. The age of 70 is the median age at diagnosis, with a slight male predominance [8].

Many risk factors have been shown to increase the incidence of MZL. In this case the major risk factors are the advanced stage Lymphoma (IIIB), age below 60 years, with the absence of other risk factors which are normally seen in similar cases such as the increase In lactate dehydrogenase, the abnormal Karnofsky score, extra-nodal involvement. This means there are 1–2 risk factors that define low-intermediate risk lymphoma according to Harrison's Hematology and Oncology [9]. Rituximab-based regimen such as bendamustine/chlorambucil is appropriate as the front-line therapy for an advanced stage MZL [3,10].

The differential diagnosis that must be considered in mind when assessing persisting or enlarged masses alongside MZL are Sarcoidosis

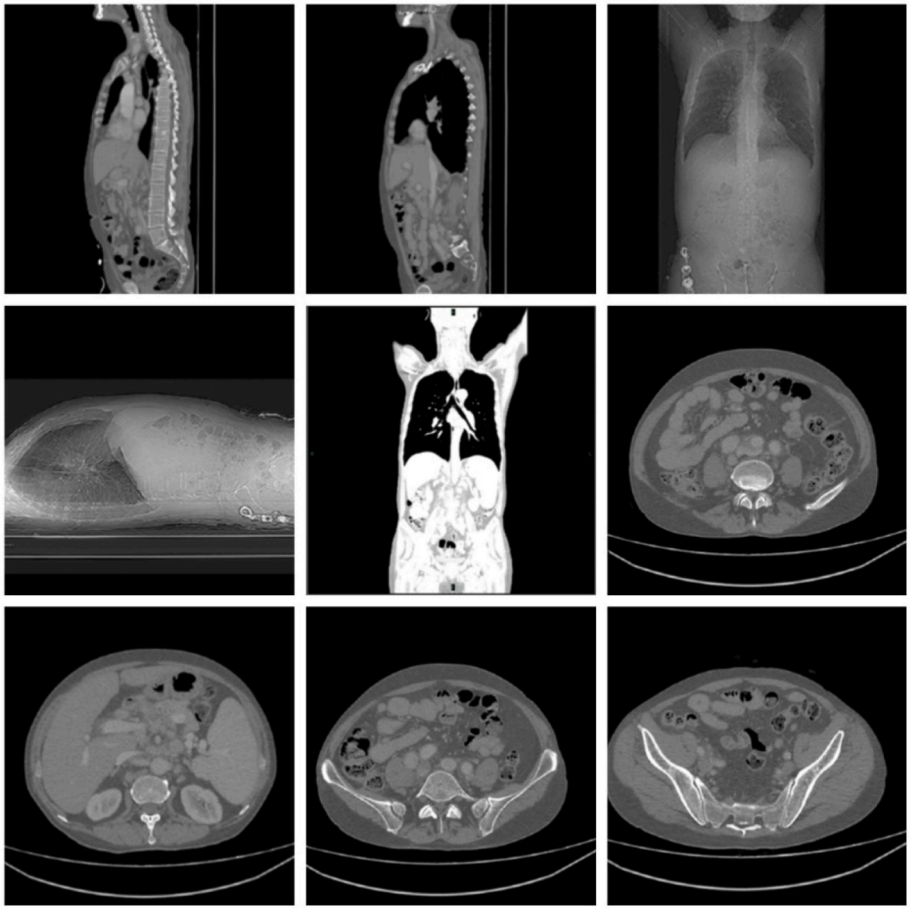

Fig. 3. Computerized tomography (CT) scan of the chest and abdomen with contrast showed emphysema, especially in the superior sections of upper lobes, nodular hyperplasia in the middle third of the right pulmonary area, and around the abdominal aorta and in the celiac group. The largest one measures 32 mm in diameter.

and Sarcoid-like reactions [11].

Sarcoidosis is a chronic systematic inflammatory disorder of unknown etiology. It mostly involves the hilar lymph nodes, lungs, and mediastinal lymph nodes [1]. The diagnosis of sarcoidosis is based on the presence of clinical radiological findings, histological features of non-caseating epithelioid cell granulomas, and the exclusion of known causes of granulomatous Inflammation [2].

Sarcoidosis and sarcoid-like reactions must be considered as possible differential diagnoses when assessing persistent or enlarged masses besides MZL [11]. The relationship between sarcoidosis and malignancies was first spotted by Brinker. It reflected a debatable subject that was fully discussed in published research in Libertas academica. Between 1962 and 1972, 48 out of 2544 patients with sarcoidosis registered in Denmark, developed solid and lymphoid malignancies compared to only 33 malicious tumors matched with age and gender in the control group. Lymphomas developed in 17 patients: eight with Hodgkin's lymphoma, nine with non-Hodgkin's lymphoma, multiple myeloma, or chronic lymphocytic leukemia. Patients with chronic sarcoidosis had an 11.5-fold incidence of lymphoma [11].

It is well-known that sarcoidosis is associated with the down-regulation of $CD8^+$ T-cells and the activation of $CD4^+$ T-cells. Which was affirmed after a conducted research showing granulomas being surrounded by CD3-positive cells, indicating the presence of T lymphocytes. CD4 marked the majority of these cells, whereas CD8-positive cells were rare, leading to the disablement of the immunoregulatory pathways and the formation of lymphoid neoplasms and noncaseating granulomata [12,13].

Sarcoidosis and Hodgkin's disease have many common immunologic aspects, both are characterized by peripheral lymphopenia, cutaneous anergy, and significant tissue infiltration of helper T-cells. Another theory hypothesizes that clinical sarcoid is a whole-body cell-mediated immune reaction to tumor antigens representing the systemic isotope of the localized noncaseating granulomata that exist within tumors [12]. Immunosuppression from chemotherapy or medicine reaction is a possible additional mechanism to the former ones. However, the occurrence of sarcoidosis after malignancy is possible without the administration of chemotherapy [11,14] as shown in a published case report in Korean J Intern Med [15].

Moreover, the inclusion of the reticuloendothelial system (lymph nodes, liver, spleen) and lymphocyte activation make a differential diagnosis between lymphoma and sarcoidosis challenging [16] A paper was published in European Respiratory Journal to define the relationship between sarcoidosis and lymphoma. Group (A) consisted of cases in which sarcoidosis is before lymphoma, group (B) consisted of cases in which the two diseases presented simultaneously (within one-month duration), and in group (C) lymphoma preceded sarcoidosis. In the previous case initial sarcoidosis findings (group A) were compared with initial lymphoma findings (group C), then sarcoidosis as the following disease (group C) was compared with lymphoma as the following disease (group A). 112 cases were initially recorded, three cases were caused by mycobacterial infection, two were drug-induced, nine cases had solid organ malignancies, and the other three had a lymphmatoid granulomatosis. One case had granulomatous angiitis, 14 exhibited SLRs, and one did not have the ATS criteria. In most of the remaining 79 cases, sarcoidosis came first (Group A, n555, 69.6%). NHL was more frequent, and the period between the two diseases was remarkably longer in group A. The distribution of sarcoidosis and lymphoma types in stages through the three categories was a homogenous. Subjects in group

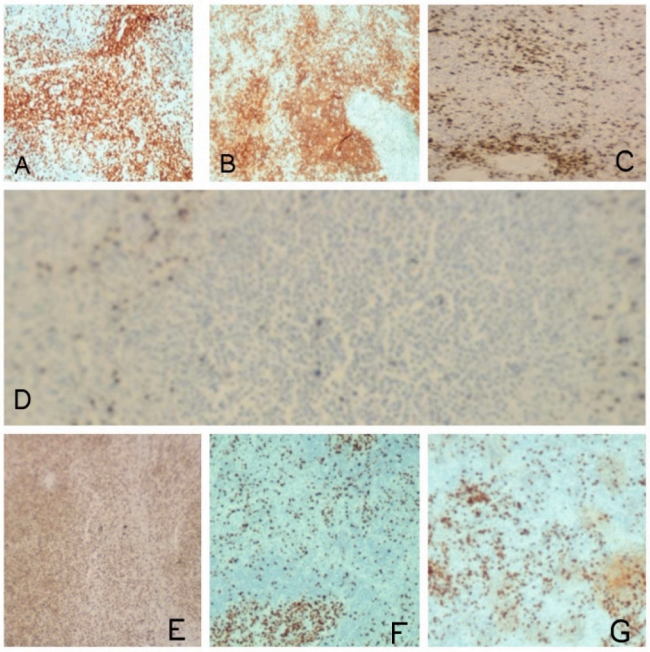

Fig. 4. Immunohistochemistry: The neoplastic cells are positive for CD 20, BCL2+ & IgD+, whereas Cyclin D1 & CD 5 & CD 3 were negative, Ki67 ~ 10%.
✓ Fig. 4/A: CD20
✓ Fig. 4/B: Bcl2
✓ Fig. 4/C: IgD
✓ Fig. 4/D: Cyclin D1
✓ Fig. 4/E: CD5
✓ Fig. 4/F: Ki67
✓ Fig. 4/G: CD3.

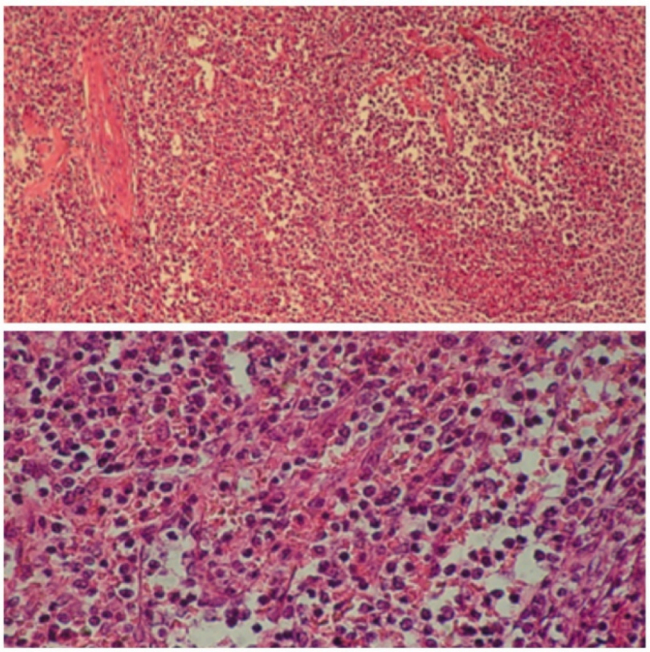

Fig. 5. Microscopic examination reveals expansion of the marginal zone by atypical small to medium –sized lymphoid cells surround and replace regressed germinal centers (H&E x 200).

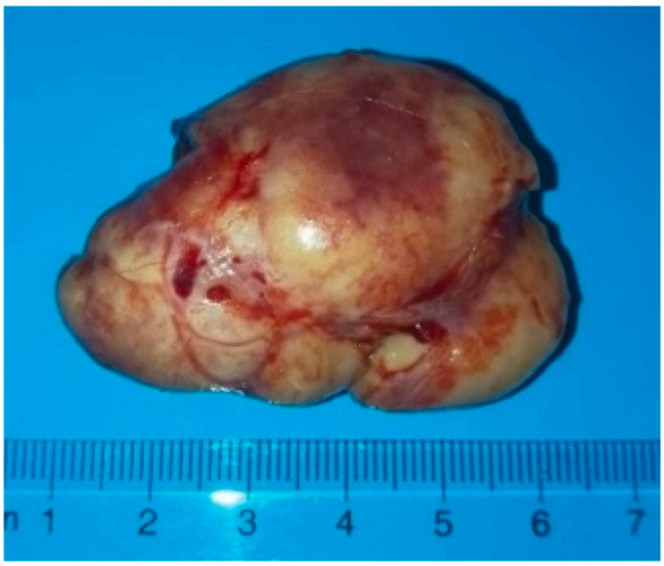

Fig. 6. Macroscopic description: rounded lymph node measuring 5 × 4 cm, gray-pink color soft to in consistency. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

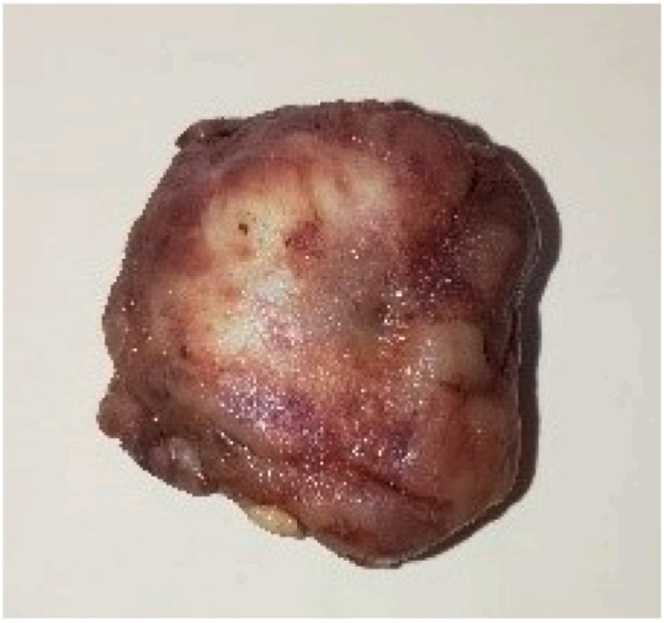

Fig. 7. Macroscopic description: An abdominal lymph node measuring 1,5 × 2 cm in maximum dimensions, gray-tan in color, soft to rubbery in consistency. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

C had a slighter organ involvement with sarcoidosis in comparison with group A [16]. As shown previously, our case goes under the third category (group C). Finally, we must mention that this work has been reported in line with the SCARE 2020 criteria [17].

4. Conclusion

In conclusion, in most cases, sarcoidosis precedes lymphomas. However, our case signified the rare occurrence of sarcoidosis after the treatment of marginal zone lymphoma. This case discussed the evidence on the possible relationship between lymphomas and the future

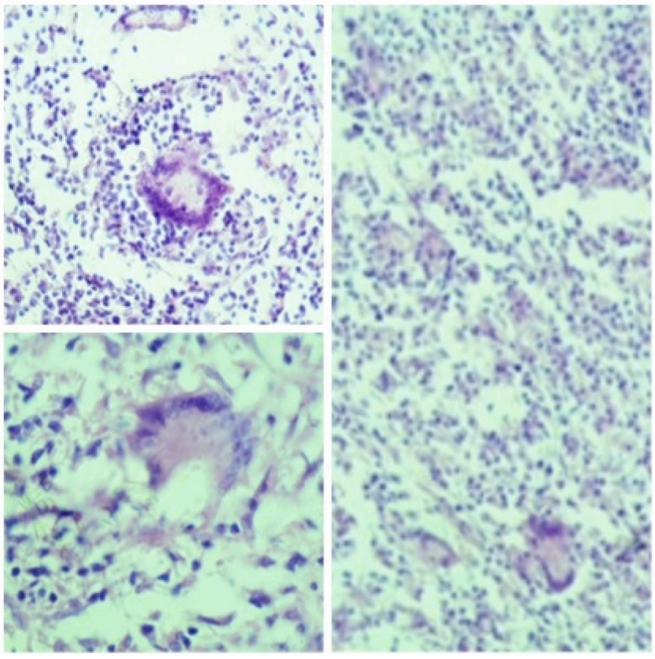

Fig. 8. The microscopic biopsy of abdominal Lymph node showed: Granulomatous lymphadenitis with Sarcoidosis No cellular atypia noted within the limits of examined specimen.

development of Sarcoidosis. Therefore we suggest to consider Sarcoidosis as a part of our differential diagnosis when following-up patients with lymphomas. A tissue biopsy is essential prior to starting chemotherapy for a presumed relapse or treatment failure in patients with MZL so as to avoid inappropriate therapy.

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

Ethical approval

This paper is a case report, therefore, ethical approval from ethics committee wasn't required.

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Authors' contribution

AS: Drafted the article, collected the patient data and managed the team.

AA: Drafted the article and collected the patient data.

ZA: the guarantor and supervisor, performed and confirmed the pathological diagnosis including immunohistochemistry, and critically revised the article.

FA: performed Chemotherapy and Sarcoidosis treatment.

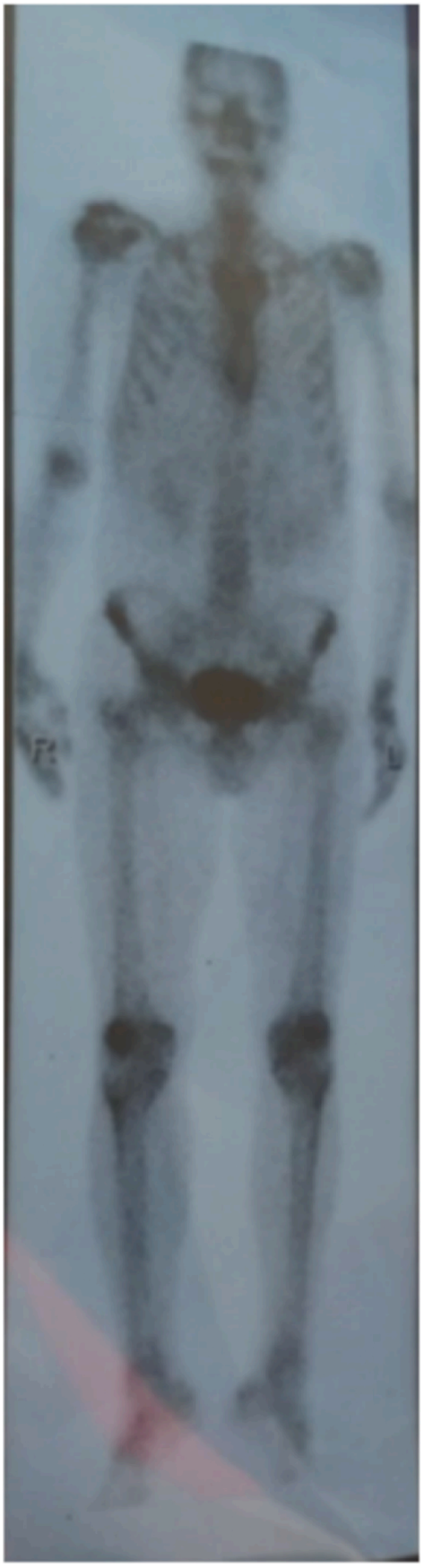

Fig. 9. 18F-FDG-PET showed mediastinal lymphadenopathy with increased fluorodeoxyglucose uptake in the abdominal nodes.

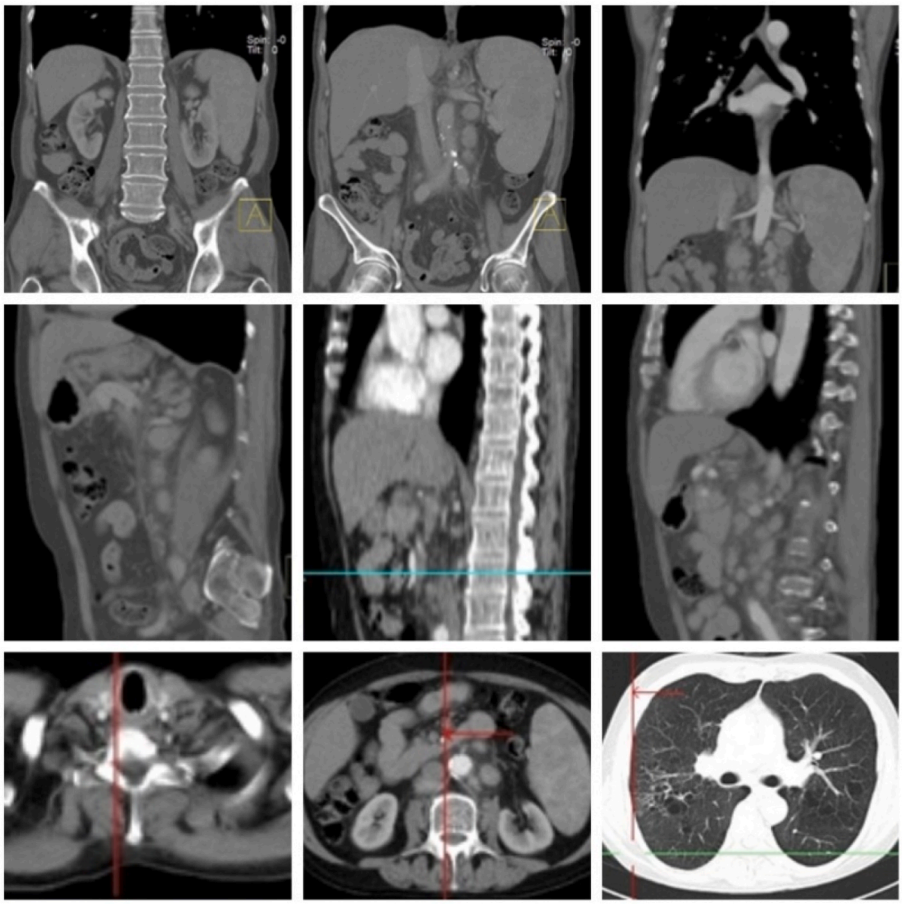

Fig. 10. CT showed a gradual recovery as the tracheal node shrank into 1 cm, the right and left navel nodes measurements reached (14mm, 9 mm respectively). A significant bilateral reticular fibrosis was recognized with the appearance of honeycomb shape. Moreover, the largest aortic lymph node measured 3 cm.

All authors have read and approved the manuscript.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-inChief of this journal on request.

Registration of research studies

Not applicable.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Guarantor

Prof. Dr. Zuheir Alshehabi.

Provenance and peer review

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Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

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