Open Access

Case Series

Autoimmune Flare after Receiving Chemotherapy in Hematological Malignancies; A Case Series and Review of Literature

Jhanzeb Iftikhar, Fareeha Sheikh, Syed Abdul Mannan Hamdani, Musa Azhar, Shafquat Ali Khan, Bushra Ahsan

Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Pakistan

ABSTRACT

Lymphoma and autoimmune diseases may share common predisposing factors. The clinical features of lymphoma patients presenting with autoimmune conditions are scarcely reported. It has been shown in some previous studies that the probability of lymphoma development may be increased on the background of autoimmune diseases. However, whether autoimmune diseases worsen the outcomes for lymphoma patients remains ambiguous. We present a case series of 3 lymphoma patients in which a rare phenomenon of autoimmune flare was noticed after receiving chemotherapy.

Keywords: Autoimmune Disease, Flare, Lymphoma, Outcome.

How to Cite This Article: *Iftikhar J, Sheikh F, Hamdani SAM, Azhar M, Khan SA, Ahsan B. Autoimmune Flare after Receiving Chemotherapy in Hematological Malignancies; A Case Series and Review of Literature. Pak Armed Forces Med J 2025; 75(Suppl-2): S375-S378.*
DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-2.6117

INTRODUCTION

The interplay between malignancy and autoimmunity is complex. The defective immune system in autoimmune disorders leads to increased risk of infections and cancers especially hematological malignancies in these disorders. However, it is difficult to infer at times whether an autoimmune disease has caused malignancy or malignancy has presented as paraneoplastic autoimmune disorder.[1]

CASE-1

A 31-year-old female presented in the medical oncology clinic with newly diagnosed stage IV diffuse large B cell lymphoma. It was recommended to offer 6 cycles of chemotherapy, followed by radiotherapy at the end. After the 4th cycle of chemotherapy, she had developed severe mouth ulcers which were treated on the lines of post-chemotherapy mucositis. She then reported new-onset pain along with pins and needles in both feet toes. She went on to develop blisters which progressed to painful ulceration along with foul-smelling discharge. On examination, there were gangrenous wounds on bilateral toes with blackish discoloration suggestive of Raynaud's phenomenon. Further examination revealed bleeding ulcers on plantar aspects of both toes and weakly palpable pulses; however, there was normal temperature and intact sensations on both feet.

Correspondence: Dr Jhanzeb Iftikhar, Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Pakistan
Received: 14 Jan 2021; revision received: 27 Apr 2021; accepted: 04 May 2021

Meanwhile, she developed new-onset eye dryness along with papular lesions on the face and neck which were mildly erythematous. The pigmented lesions were around the eyebrow, nasal bridge, and in the perioral territory. However, there was no history of joint/muscle pain, recurrent oral ulcers, or skin rash before the diagnosis of lymphoma. In the context of the clinical picture, the following differentials were considered:

1- Mixed connective tissue disease.

2- Large vessel occlusion.

3- Small vessel vasculitis.

4- Infective/cellulitis.

5- Cryoglobulinemia.

6- Drug-induced.

CT angiogram did not show any occlusion or intimal calcification in the bilateral lower limb arterial tree. Autoimmune profile revealed following results:

Positive antinuclear antibody (>/=1:5120).

Normal Rheumatoid Factor.

Negative anticardiolipin antibody Ig G,A,M.

Normal cytoplasmic antineutrophilic antibody, c-ANCA and perinuclear-ANCA.

Anti SS-A (Ro): strong positive Anti SS-B (La): strong positive.

Anti Scl-70: borderline Anti Ro-52: strong positive.

Negative for anti dsDNA, anti-Sm, anti-RNP, anti-Jo-1, anti-centromere, anti-Histone.

Normal complement C3 and raised complement C4; 65 mg/dL (normal range: 15-45 mg/dL).

Further laboratory profile indicated:

Activated Partial Thromboplastin Time 28.9 Seconds (normal range: 24.5-35.2 sec).

Mildly raised urinary albumin/creatinine ratio 38.57 mg/g (normal value: 10 mg/g).

Raised C-reactive protein 34 mg/l (normal value: <10 mg/L).

No pathogens were isolated on blood culture.

Thereafter, she was managed by a rheumatologist on lines of Sjogren's syndrome. Optical coherence tomography was done which showed macular thinning. Given the insidious onset of Sjogren's syndrome, chemotherapy had to be held after cycle 4. She was started on hydroxychloroquine with significant recovery in face, hand, and feet lesions; however, feet ulcers were in the healing phase. Unfortunately, she went on to develop hemo-phagocytic lymphohistiocytosis (HLH) syndrome (Figure 1a-d) and died of it.

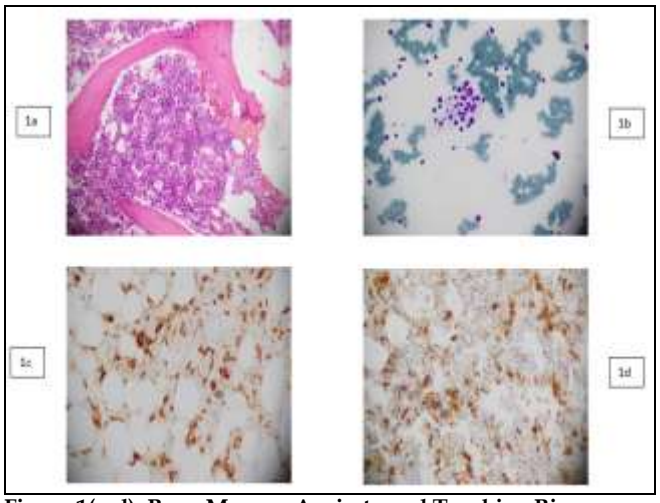

Figure 1(a-d): Bone Marrow Aspirate and Trephine Biopsy Images

1a: Increased number of macrophages scattered among the normal hematopoietic precursors
1b: Cytophagic histiocyte identified in the aspirate
1c,d: Immunohistochemical staining for cd 68 revealing increased macrophages

CASE-2

A 31-year-old male was planned to be commenced on chemotherapy for his treatment naïve stage IV nodular sclerosis classic Hodgkin's lymphoma. He was a welder by profession and had a 15 pack-year history of smoking. After the 1st cycle of chemotherapy, he developed complaints of discoloration, pain, and numbness in the left-hand fingers particularly in the pulp of the index and middle finger. He was unable to hold things in the left hand. Examination revealed bluish discoloration and severe tenderness in left-hand index and middle fingers which were cold to touch. Left brachial and radial pulses were weak in comparison to right upper limb pulses; however, there was no sensory loss. Keeping in view the clinical presentation, differentials were:

Thromboangiitis obliterans/Buerger's disease (related to his smoking history).

Cold agglutinin disease (autoimmune association with lymphoma).

Raynaud's syndrome (association with smoking, welding occupation (vibration) and chemotherapy (bleomycin, vincristine, doxorubicin).

Vascular insufficiency/cardiac embolism/arterial thrombi.

Cryoglobulinemic vasculitis.

Arterial Doppler ultrasound of left upper extremity was done which was negative for arterial stenosis or occlusion. Echocardiography was done to rule cardiac embolic phenomenon which was also normal. Autoimmune profile was turned out to be normal; complement C 3 (107 mg/dL) (normal range: 90-180 mg/dL), C 4 (16mg/dL) (normal range: 15-45 mg/dL), antinuclear antibodies (negative), lupus anticoagulant LA1 (39.9 seconds), anticardiolipin IgG,A,M (0.239), peri-nuclear antineutrophilic cytoplasmic antibody (p-ANCA)(U/mL), cytoplasmic-ANCA (0.71 U/mL) and antimitochondrial antibodies M2 (<1 U/mL).

Nifedipine, low molecular weight heparin, and aspirin were commenced. He was given advice regarding wearing hand gloves to keep warm and smoking cessation; however, he continued to smoke. He was then followed up by a rheumatologist who managed him on lines of Buerger's disease. Thereafter, his finger ischemic symptoms started to resolve.

From a lymphoma standpoint, his chemotherapy was further complicated with delay due to drug-induced hepatitis (liver biopsy-proven). Unfortunately, he encountered disease progression for which he is currently receiving salvage chemotherapy.

CASE-3

A 34-year-old male presented with newly diagnosed stage IIIB mixed cellularity Hodgkin's Lymphoma. At presentation, there was a 10-month history of fever, difficulty in walking, lower limb

throbbing pain and bilateral inguinal swellings. He was wheel chair bound at presentation and his past medical history was notable for pyelonephritis. Lower limb revealed bilateral ankle swellings, hair loss along with ulceration and discoloration at malleolar region. Distal pulses were palpable along with normal temperature and intact sensations of lower limb.

Considering the clinical presentation, differentials were:

Cellulitis.

Ischemic ulcers.

Deep vein thrombosis (DVT).

Vasculitis (polyarteritis nodosa, Churg-Strauss syndrome, Buerger's disease and microscopic polyangiitis).

Peripheral venous doppler ultrasound was negative for DVT. Peripheral arterial doppler ultrasound showed good triphasic flow in distal vessels and there was no evidence of luminal stenosis or arterial thrombosis in bilateral lower limb vessels. Autoimmune blood profile showed mildly raised complement C4 (41mg/dL) (normal range: 15-45 mg/dL), normal complement C3(157mg/dL) (normal range: 90-180 mg/dL) and negative anti-nuclear antibodies along with normal perinuclear anti-neutrophil cytoplasmic antibodies, p-ANCA (1.55U/mL) and cytoplasmic-ANCA (2.14U/mL).

He showed some improvement after initial supportive treatment. Thereafter, chemotherapy was commenced for lymphoma. He received chemotherapy uneventfully in the beginning; however, there was an increase in size of leg ulcers along with purulent discharge after the 3rd cycle of chemotherapy. X-ray of the left leg showed a heterogeneous soft tissue thickening overlying the anterolateral aspect of the distal left leg and ankle extending to the skin suggestive of an ulcerating wound; however, bone was intact. C-reactive protein was raised (44mg/L) and culture wound swab revealed heavy growth of Escherichia coli after 48 hours. Antibiotics were advised by infectious disease consultant for his chronic non-healing infected ulcer. To rule out squamous cell cancer lesion, multiple incisional biopsies were taken by the plastic surgeon, which were suggestive of inflammatory changes without any evidence of malignancy. Left foot wound became large (6x5cm) with undermined edges in front of left shin.

Chemotherapy had to be stopped for some time until improvement of the left leg. Chemotherapy was then restarted after a delay and he went on to complete 6 cycles of chemotherapy with a good response in the end of treatment scan. Since then, he has been on surveillance and is on active follow up.

DISCUSSION

The precise pathogenesis of lymphoma is unclear. The potential risk factors include infection, immunodeficiency, and autoimmune diseases. Association of Epstein–Barr virus infection with Burkitt or natural killer/T cell lymphoma is well recognized. Furthermore, eradication of H. pylori is now considered to be the standard of care for H. pylori-positive mucosa-associated lymphoid tissue (MALT lymphoma).

The prevalence of lymphoproliferative malignancies, particularly NHL in autoimmune disorders is around 5%. The association of lymphoma with autoimmunity is interesting because of rare co-occurrence.[2] Connective tissue diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjogren's syndrome (SS) have two-to-five fold increased risks of developing lymphoma.[3,4] Autoimmune diseases and lymphoma may share common risk factors. There is also an increased prevalence of autoantibodies in the cancer patients which also points towards a link between cancers and autoimmune diseases.

Although the basic pathophysiology is not known, a strong correlation between RA and diffuse large B cell lymphoma (DLBCL) has been reported by Varoczy *et al.,* and Bernatsky *et al.*[5] A proliferation-inducing ligand (APRIL) might be the causal element. Interestingly, DLBCL cells have increased APRIL expression in comparison to other types of lymphoma.[6] Additionally, a higher level of APRIL has been supposed to be associated with the development of RA and SLE. SS has also been reported to be associated with mucosal-associated lymphoid tissue (MALT) lymphoma.[7] RA development in HL patients could be associated with chronic inflammation caused by EBV.[8]

The exact cause of autoimmune flare in our patients is unclear. However, chronic inflammation leading to B or T cell reactivation and antigenic stimulation due to autoimmunity could have played a decisive role in the pathogenesis of lymphomas.[9,10]

In conclusion, the relationship between autoimmunity and lymphoma is bi-directional. More prospective studies are needed focusing on the association between certain histologic lymphoma subtypes and specific autoimmune diseases to understand the impact of autoimmunity on the outcome of lymphoma.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

JI & FS: Data acquisition, data analysis, critical review, approval of the final version to be published.

SAMH & MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SAK & BA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1- Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders–what are the driving forces? InSeminars in cancer biology 2014: 24: 61-70.

2- Van den Bergh M, Alvarez-Argote J, Panwala AH, Dasanu CA. Autoimmune disorders in patients with T-cell lymphoma: a comprehensive review. Curr Med Res Opin 2015; 31(10): 1861-1870.

3- Hellgren K, Baecklund E, Backlin C, Sundstrom C, Smedby KE, Askling J. Rheumatoid arthritis and risk of malignant lymphoma: is the risk still increased? Arthritis Rheumatol 2017; 69(4): 700-708.

4- Fragkioudaki S, Mavragani CP, Moutsopoulos HM. Predicting the risk for lymphoma development in Sjogren syndrome: an easy tool for clinical use. Med 2016; 95(25).

5- Váróczy L, Páyer E, Kádár Z, Gergely L, Miltényi Z, Magyari F, et al. Malignant lymphomas and autoimmunity—a single center experience from Hungary. Clin Rheumatol 2012; 31(2): 219-224.

6- Löfström B, Backlin C, Pettersson TO, Lundberg IE, Baecklund E. Expression of APRIL in diffuse large B cell lymphomas from patients with systemic lupus erythematosus and rheumatoid arthritis. The Journal of rheumatology 2011; 38(9): 1891-1897.

7- Papageorgiou A, Ziogas DC, Mavragani CP, Zintzaras E, Tzioufas AG, Moutsopoulos HM, et al. Predicting the outcome of Sjogren's syndrome-associated non-Hodgkin's lymphoma patients. PloS one 2015; 10(2): e0116189.

8- Hollander P, Rostgaard K, Smedby KE, Chang ET, Amini RM, de Nully Brown P, et al. Autoimmune and atopic disorders and risk of classical Hodgkin lymphoma. American journal of epidemiology 2015; 182(7): 624-632.

9- Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmunity reviews 2017; 16(10): 1049-1057.

10- Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Archives of internal medicine 2005; 165(20): 2337-2344.