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Recurrence of Non-Hodgkin Lymphoma at the Insulin Injection Site: Case Report

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Abstract—**This study sheds light on the effect of insulin, insulin-like growth factors (IGF), and their signalling receptors (IR and IGF-1R) on the progression of lymphoma. We report a case of a 64-year-old male with type 2 diabetes mellitus and a prior diagnosis of diffuse large B-cell non-Hodgkin lymphoma (DLBCL) treated with chemotherapy and local radiotherapy. Incredibly, four years post-treatment, the patient's DLBCL relapsed in the subcutaneous fatty tissue adjacent to the deltoid muscle of both the proximal left and right upper extremities, which were the sites he used to inject insulin. Insulin/IGF dysregulation can lead to tumour growth via angiogenesis. This mechanism is not limited to lymphoma and may contribute to the development of various types of cancer. While it is possible that DLBCL may have developed at the injection site either coincidentally, as a result of chronic inflammation, or potentially due to other factors that promote tumour growth, as we suggest in our case presentation, it is beneficial to emphasise the importance of tumour screening in diabetic patients, especially those receiving insulin injections. We therefore believe that regular screening of the insulin injection site should be included in routine consultations for these patients.**

Index Terms— **Insulin; Insulin-like growth factor; Lymphoma; Neoplasm; Non-Hodgkin; Regular.**

I. INTRODUCTION

Lymphoma is a broad term comprising many cancers with lymphatic origin. Although the classification of lymphoma is detailed, it is first divided into non-Hodgkin (NHL) and Hodgkin lymphoma (HL). More than 500,000 cases of NHL are diagnosed every year, making it the most common haematological cancer worldwide [1]. It constitutes 90% of all lymphomas, with the remaining 10% being HL [2]. Moreover, NHL has many histological varieties, the most common being diffuse large B cell (DLBCL), which accounts for 30% of NHL. In addition to that, variation is also seen among clinical presentations. Patients typically present with a fast-growing painless mass of cervical, mediastinal, or abdominal lymph nodes, thus usually presenting in advanced stages. On the other hand, one-third of patients are symptomatic for B symptoms (fever, night sweats, and weight loss) [3]. Frequently presenting in men, with an average age at presentation of 53.56 ± 17.95 years [4], DLBCL is an aggressive tumour that is fatal within months if left untreated; however, two-thirds of patients are curable with proper and timely treatment [5]. Over 50% of patients can be cured using multi-agent chemotherapy, radiotherapy, and/or immunotherapeutic drugs, combined with or without autologous stem cell transplant. Unfortunately, despite appropriate treatment, relapse is fairly common, presenting in 30-40% of patients, making it the leading cause of morbidity and mortality [6]. Lymphomas, or neoplasms generally, can arise from the dysregulation of the insulin/insulin-like growth factor (IGF) signalling pathways, and studies have shown a relationship between insulin receptors and tumour development [7]. Moreover, insulin receptors and IGF-1R (recep-

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tors of IGF) have a very similar sequence and structure; thus the increase of both insulin and IGF have been significantly associated with the development of neoplasm [8].

II. CASE PRESENTATION

Our patient is a 64-year-old male, previously diagnosed with diffuse large B-cell non-Hodgkin lymphoma (DLBCL). He presented with pain in his upper left arm. His medical history includes coronary bypass surgery, cholecystectomy, cataract surgery, and insulin-treated diabetes mellitus. He is an ex-smoker with a history of 53 pack-years and used to consume alcohol.

The patient was initially diagnosed with stage IIA large B-cell lymphoma in 2012, confirmed by an excisional biopsy of the tongue root. Immunohistochemical and histomorphological findings were consistent with DLBCL (Figure 1). He underwent chemotherapy (R-CHOP) and adjuvant radiotherapy (IFRT—involved-field radiotherapy) in 2012 and 2013. The chemotherapy regimen included MabThera (rituximab) at 375 mg/m², Endoxan (cyclophosphamide) at 750 mg/m², doxorubicin at 50 mg/m², Oncovin (vincristine) at 1.4 mg/m², and Mesna (uromitexan) at 750 mg/m². After four cycles of R-CHOP, the patient achieved complete remission and continued with four additional cycles of MabThera.

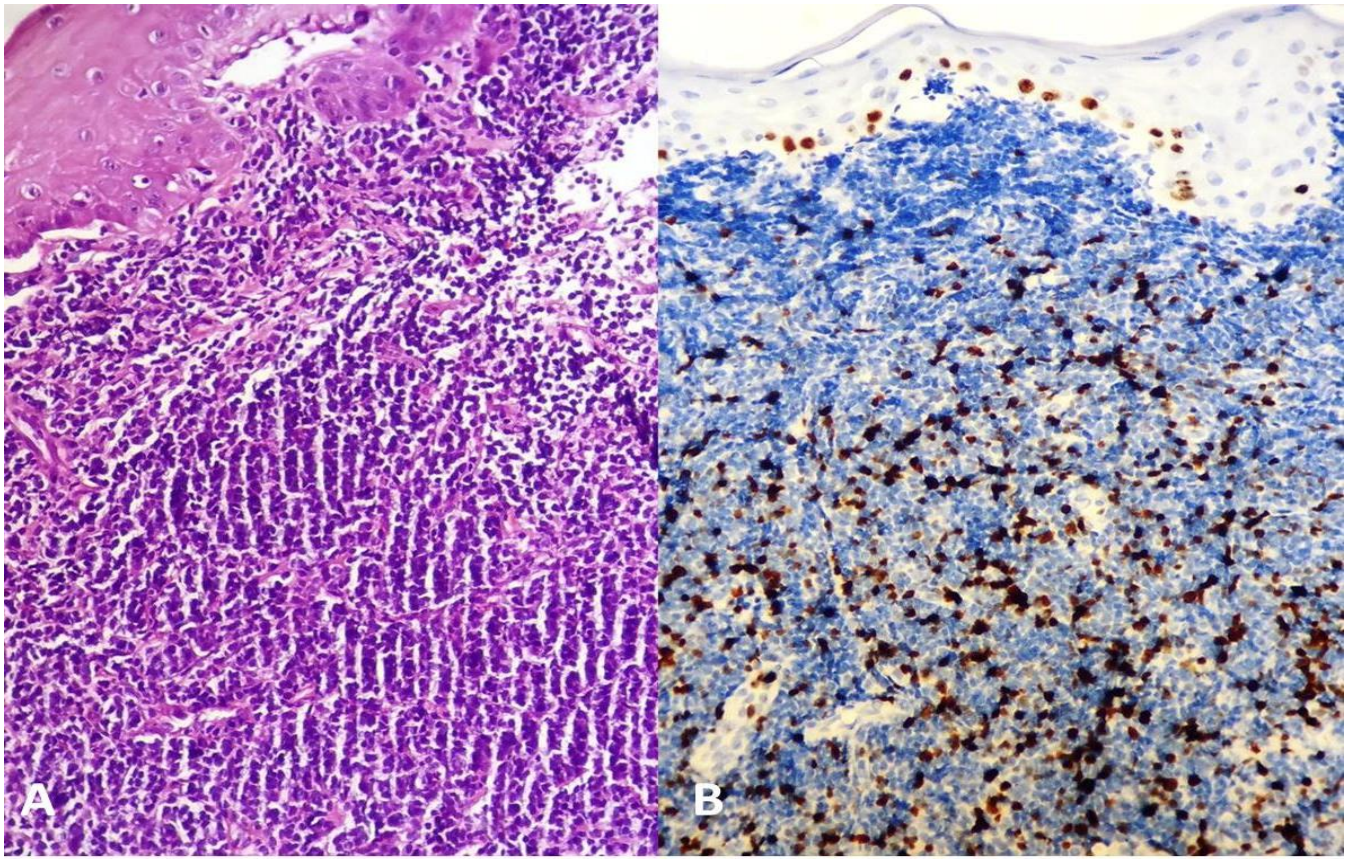

Figure1. A: Atypical lymphoid infiltration under tonsillar squamous epithelium, H&E stain, magnification x200. B: High proliferative index infiltration under the epithelium in the tonsil biopsy sample, MIB-1 immunohistochemistry, DAB chromogen, magnification x200.

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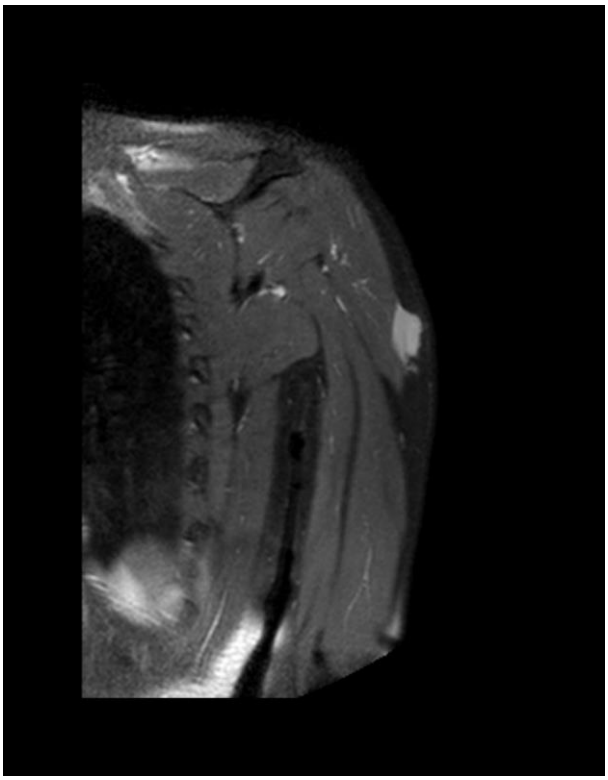

Figure 2. The Large Lesion - Coronal Section

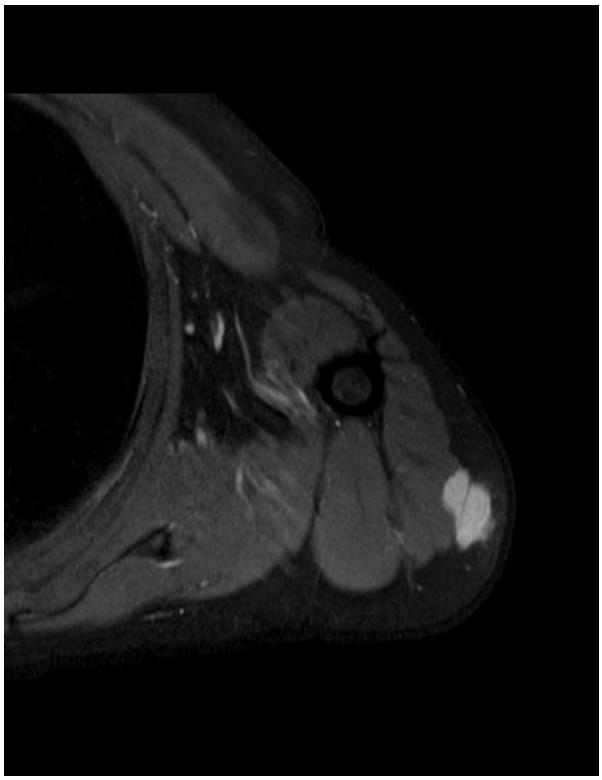

Figure 3. The Large Lesion – Transverse Section

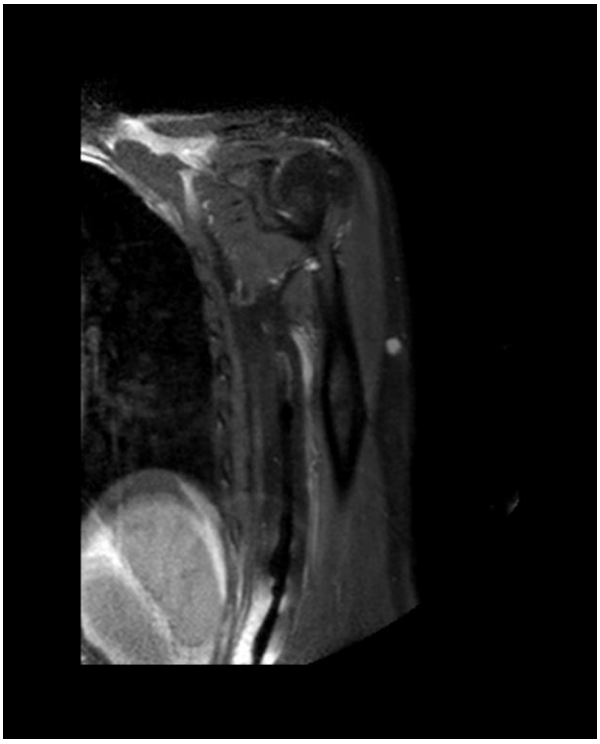

Figure 4. The Small Lesion – Coronal Section

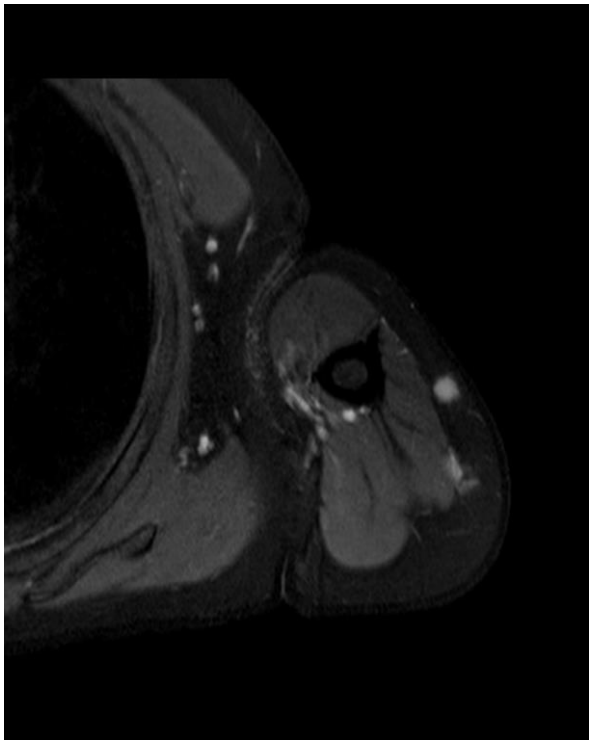

Figure 5. The Small Lesion – Transverse Section

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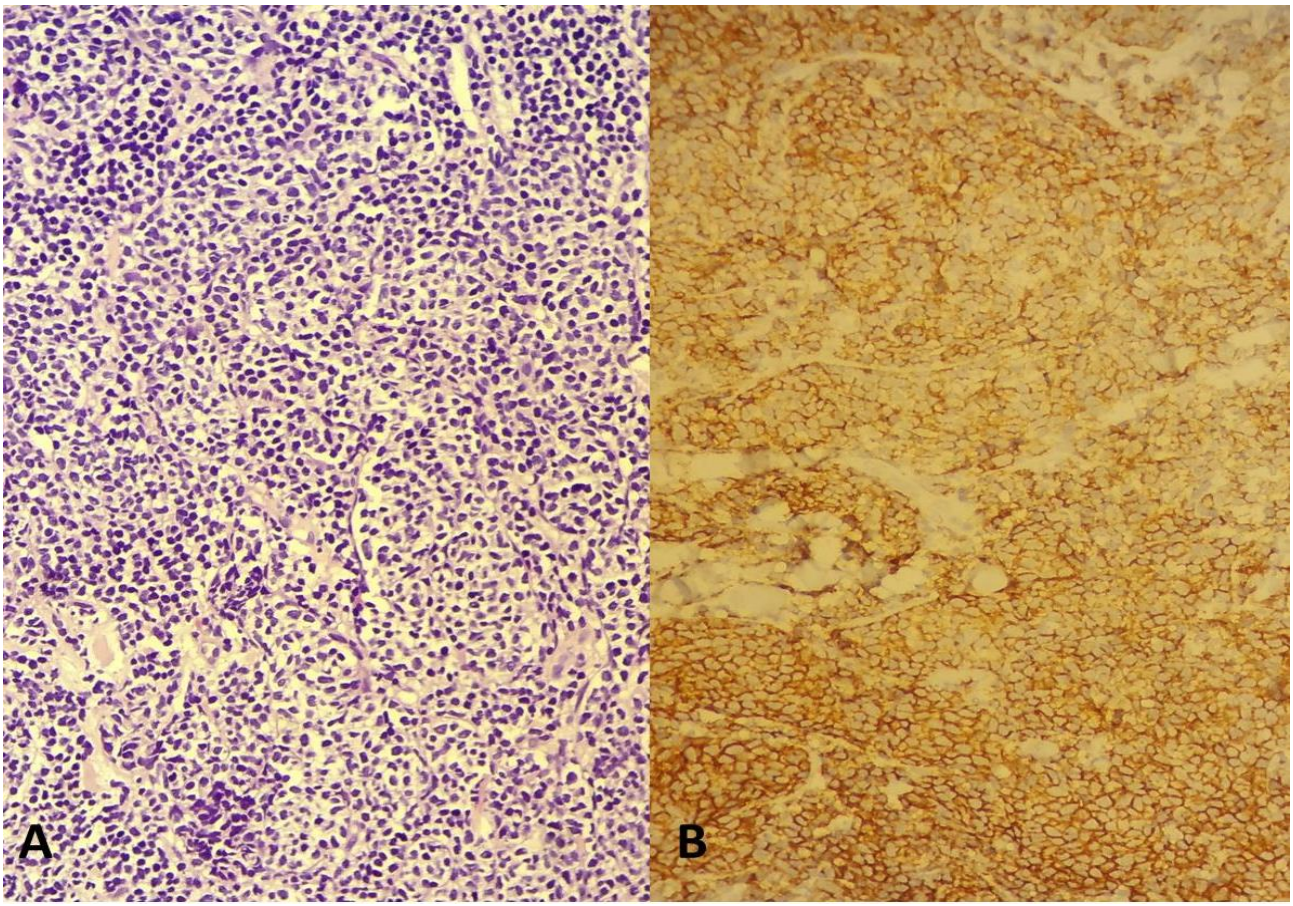

Figure 6. A: Atypical lymphoid infiltration in skin tru-cut biopsy sample, H&E stain, magnification x200. B: Atypical lymphoid infiltrate in skin tru-cut biopsy sample, CD20 immunohistochemistry, DAB chromogen, magnification x200.

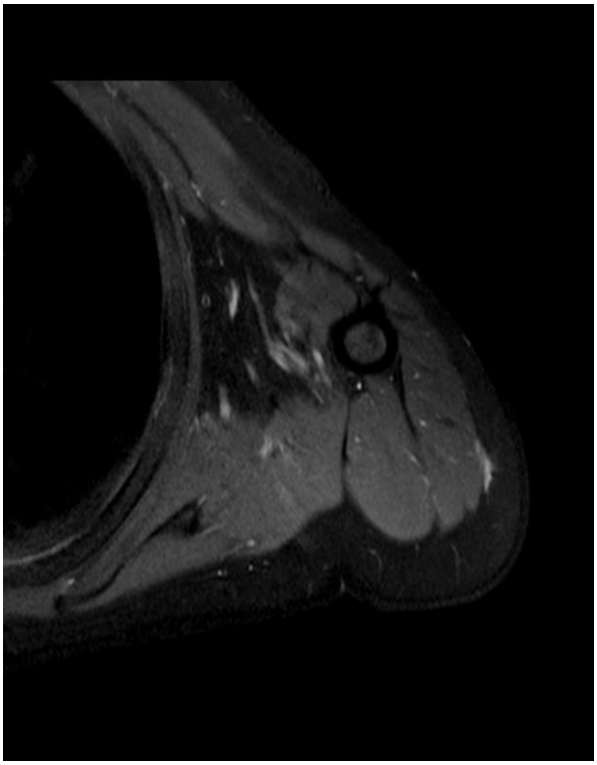

Figure 7. The Large Lesion After Therapy -Transverse View

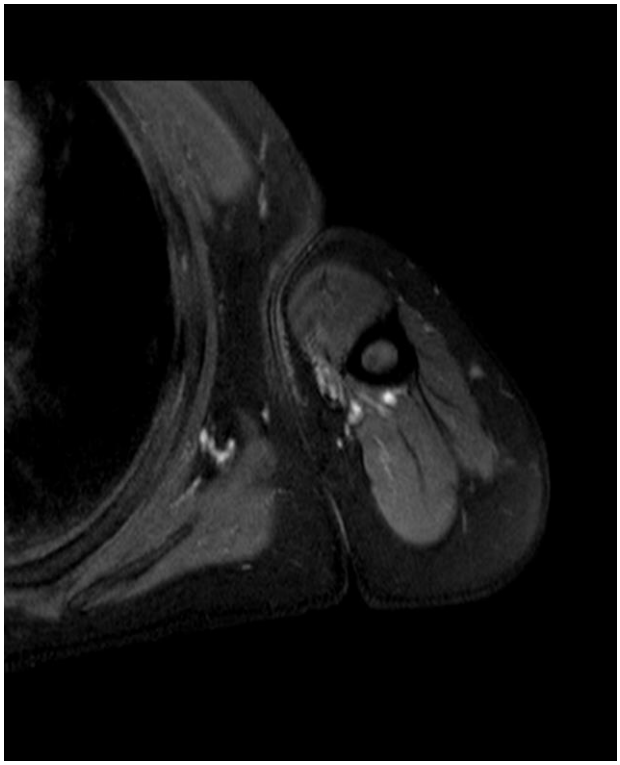

Figure 8. The Small Lesion After Therapy – Transverse View

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In 2015, a F-18 PET-CT scan revealed two soft tissue lesions with high metabolic activity in both upper extremities: one larger lesion on the left (22 mm, SUV max: 4.58) and a smaller lesion on the right (13 mm, SUV max: 3.57). In response, he received another four cycles of R-CHOP followed by two cycles of MabThera.

In 2016, the patient reported pain in his upper left arm, leading to further investigation. An MRI of the humerus with IV contrast revealed a nodular lesion (7 mm) in the subcutaneous fatty tissue adjacent to the deltoid muscle, along with a larger irregular lesion (34 x 26 x 17 mm) causing contour lobulation in the deltoid. Both lesions showed T1 hypo-intensity and significant post-contrast uptake, raising suspicion for metastasis given the patient's history of lymphoma (Figures 2, 3, 4 and 5). A tru-cut biopsy of the left upper extremity confirmed lymphoma infiltration consistent with DLBCL (Figure 6).

In response to this recurrence, he underwent chemotherapy and adjuvant radiotherapy (IFRT) again in 2016. The chemotherapy regimen consisted of cisplatin at 100 mg/m² and Cytarabine (cytosine arabinoside) at 750 mg/m² for three cycles.

Later the same year (2016), a follow-up MRI with IV contrast revealed a 3 mm-diameter nodular lesion in the subcutaneous fatty tissue adjacent to the deltoid muscle of the proximal left upper extremity. Additionally, a posterior irregularly contoured lesion measuring 19 x 4 mm was observed in the same region. Both lesions continued to exhibit T1 hypointensity, with similar post-contrast findings indicating potential metastatic involvement. However, compared with the MRI results from earlier that year, a marked regressive decrease was observed in the sizes of the lesions, as shown in Figures 7 and 8. Furthermore, no malignancy was detected on the right upper extremity.

III. DISCUSSION

Insulin resistance, hyperglycaemia, and hyperinsulinaemia are important components of type 2 diabetes mellitus (T2DM) that aid the development of neoplasms. Insulin/IGF signalling regulates cellular viability; thereby dysregulation induces neoplasia. Insulin and insulin-like growth factor (IGF) are responsible for multiple cellular functions, including glucose metabolism, proliferation, differentiation, and survival. Both activate the same pathways comprising phosphoinositide 3-kinase (PI3K) and AKT, or RAS, and MAP kinase, which conduct diverse cellular stimulations. The insulin and IGF mechanism is a complex system consisting of ligands, receptors, and signalling pathways. Our study emphasises the importance of considering the possibility of tumour progression when prescribing insulin or insulin-associated therapies; most importantly, the progression of lymphoma. We deduce the need to screen diabetic patients, particularly those who are prescribed insulin injections, for tumour growth, and especially lymphoma, at the injection sites. Recent studies have identified a connection between cancer growth and T2DM. It was ascertained that type 2 diabetes is a growing global epidemic associated with an increased risk of cancer and increased cancer-related mortality [9]. Studies using diabetic non-obese mice demonstrated the link between diabetes and the development and metastasis of tumours dependent on insulin and insulin growth factor-1 (IGF-1) [10-11]. Moreover, T2DM predisposes individuals to tumour growth; adding to this the use of insulin increases the risk of lymphoma, as seen in the case of our patient. Investigations into insulin receptors (IRs) have substantiated a relationship between IRs and tumour development, where IGF-1R is also involved in neoplasm genesis. Elevated IR expression was established in human breast cancer compared with normal breast tissue [12], and different studies have demonstrated that IRs are exaggerated in thyroid, colon, and ovarian malignancies [13-15]. Investigations into these kinds of human adenocarcinoma showed raised numbers of IRs on the endothelial cells, establishing an association between surplus IR and angiogenesis. Furthermore,

in-vitro angiogenesis experiments that tested specific commercially valid insulin products demonstrated that insulin has the potential to enhance the capillary-like tube manufacture of human microvascular endothelial cells; thus, IR overexpression is associated with angiogenesis and may be the main driving factor for the development of tumours in certain types of adenocarcinoma where IR was also concurrently increased. It is important to clarify that, while previous studies have indicated that metastatic disease or tumour growth can arise from mechanisms such as chronic inflammation due to repetitive administration of subcutaneous injections at a specific site [16], we hypothesise that the similarity between insulin and IGF pathways may also play a role. Specifically, this similarity could contribute to the upregulation of IRs and enhanced angiogenesis in the cells of the upper extremities, where our patient administered insulin. This interaction may have facilitated the development of lymphoma in these regions. Through this case report, we wish to highlight the importance of screening for diabetes mellitus patients, particularly those undergoing insulin therapy, due to the potential risk of developing tumours such as lymphoma. Furthermore, existing literature suggests that insulin resistance is a significant risk factor for poor prognosis in patients with DLBCL.

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