The rare case of synchronous multiple primary malignancies of invasive ductal carcinoma and diffuse large B-cell lymphoma in a single patient: A diagnostic conundrum

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SUMMARY

Synchronous multiple primary malignancies (SMPMs) denote the discovery of a second primary cancer within 6 months detection of a first primary cancer. Herein, we illustrate a rare case of SMPMs in a 62-year-old lady who had initially been diagnosed with primary breast invasive ductal carcinoma. A left mastectomy with axillary clearance was performed following a biopsy of a left breast lesion revealing an extensive high nuclear-grade ductal carcinoma in situ. Unfortunately, she presented to us with new complaints 2 months later with right lymphadenopathy and constitutional symptoms for a month. Excisional biopsy of a right cervical node was confirmative of a diffuse large B-cell lymphoma. She responded well to Rituximab–Cyclophosphamide–Doxorubicin–Vincristine–Prednisone (R-CHOP) regime for one cycle, followed by R-CHP regime for five cycles regimen. The presence of dual primary malignancies within 6 months fulfilled the diagnosis of SMPM in our patient. The clinical quandary in such cases may influence the diagnostic approach and treatment options. Hence a thorough clinical assessment and histopathological staging of both malignancies, as well as interdisciplinary team discussions, are essential.

INTRODUCTION

Multiple primary malignancies (MPMs) were initially described in 1889 by Billroth and reported in 1932 by Warren and Gates.[1] MPMs are defined as the presence of two or more distinct histological malignancies in the same person. Based on the time of diagnosis, MPMs can be further divided into two categories; synchronous multiple primary malignancies (SMPMs) are when the second primary cancer is diagnosed within 6 months, while metachronous multiple primary malignancies (MMPMs) are whenever the second primary cancer is diagnosed after 6 months detection of the first primary cancer. In order to establish the diagnosis, these two malignancies should not be due to tumour recurrence, metastasis, or local spread.[2]

SMPMs combination of a solid and haematological cancers are uncommon. For example, the simultaneous occurrence of a primary breast cancer and lymphoid tissue malignancy has rarely been reported in the literature,[3] though breast cancer is the most commonly diagnosed malignancy following treatment for Hodgkin's lymphoma.[4] Herein, we report a rare case of SMPMs involving an elderly women diagnosed with diffuse large B-cell lymphoma (DLBCL) who had been diagnosed with primary breast invasive ductal carcinoma 2 months prior. We aimed to highlight the diagnostic dilemma and therapeutic approach in our case, as well as provide a comprehensive discussion on the prevalence, risk factors and management approach in MPMs to promote awareness among clinicians on this unusual clinical condition.

CASE PRESENTATION

This is a case of a 62-year-old lady who presented with prolonged intermittent fever associated with cough, lethargy, marked loss of appetite and weight of nearly 8 kg for over a month with no night sweat. Her hypertension and dyslipidaemia were well controlled on medications, and she was on sulfasalazine prescription only for the past 18 years for rheumatoid arthritis. She neither smoked nor was she an alcoholic, however had a strong family history of lung cancer in her immediate family. Despite the completion of two courses of oral antibiotics, her symptoms persisted. Physical examinations were unremarkable.

Routine blood tests were equivocal with no derangement in full blood count parameter (white blood cell 4.85 × 10^3/uL, haemoglobin 12 g/dL, platelet 199 × 10^3/uL). Viral infective screening for human immunodeficiency virus (HIV), hepatitis B and hepatitis C, as well as acid-fast bacilli screening, were all negative. C-reactive protein (CRP) was raised (44.9 mg/L) but blood culture and sensitivity revealed no growth and she was afebrile in ward. However, lactate dehydrogenase (LDH) (2150 U/L), erythrocyte sedimentation rate (40 mm/Hr), and Ca-125 (2714.8 U/ml) were significantly elevated. Screening with abdominal ultrasound showed multiple nodular

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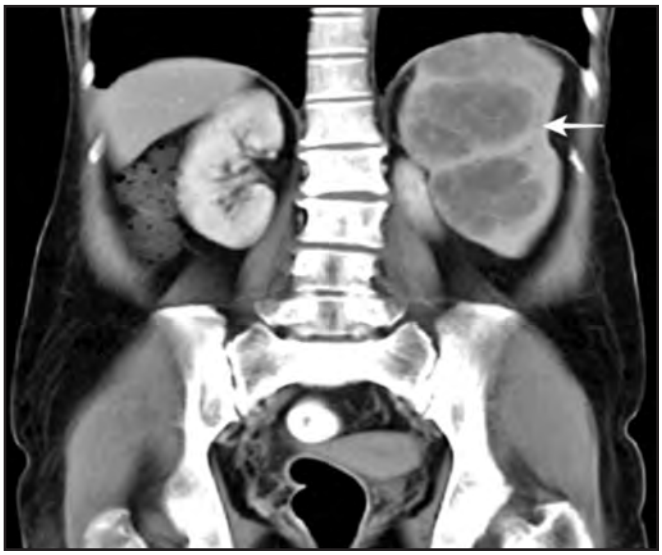

Fig. 1: Contrast-enhanced CT thorax, abdomen, and pelvis image. Multiple hypodense splenic lesions of varying sizes, with the largest measuring 5.4 cm × 6.8 cm

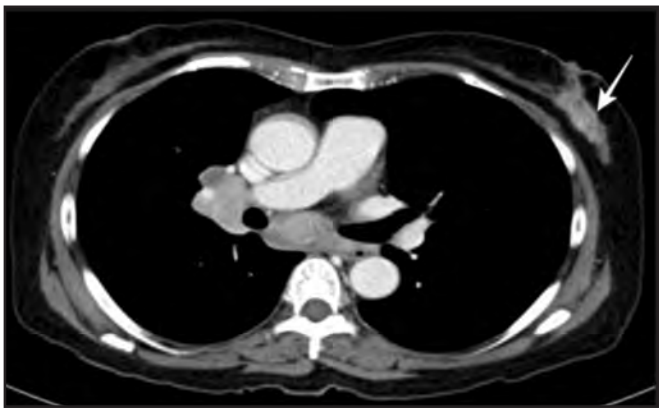

Fig. 2: CT scan image. An ill-defined enhancing lesion at the outer quadrant of the left breast

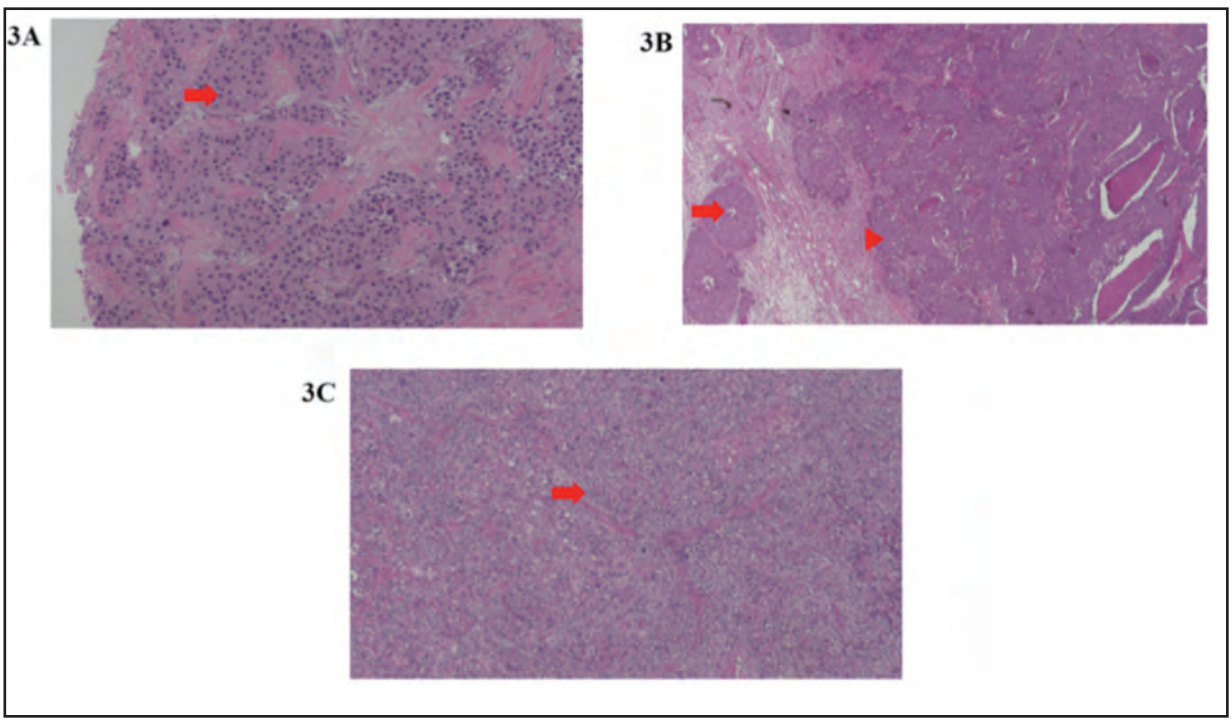

Fig. 3: Histopathological images. (A) Tru-cut biopsy of the breast showed extensive DCIS, composed of malignant cells with moderate to marked nuclear atypia filling the ducts (red arrow) with preserved myoepithelial lining (Haematoxylin & Eosin (H&E), 10×). (B) The mastectomy resection revealed multifocal invasive ductal carcinoma (read arrow head) in the background of extensive DCIS of moderate to high nuclear grade (red arrow) with central comedonecrosis and microcalcification (H&E, 4×). (C) Biopsy of the right lymph node showed diffuse and large malignant lymphoid cells (red arrow) with predominantly atypical centroblasts (H&E, 4×)

hypoechoic lesions within the spleen, with the largest measuring 5.8 cm × 4.4 cm. Differential diagnoses at that point include splenic abscess or a primary splenic tumour (lymphoma) or a splenic metastasis. She was empirically treated for splenic abscess with intravenous ceftriaxone. Subsequent contrast-enhanced computed tomography of the thorax, abdomen and pelvis confirmed the presence of multiple ill-defined splenic nodules that were detected on ultrasound. The largest nodule measures 5.4 cm × 6.8 cm (Figure 1). The lesions appeared heterogeneous with enhancing septae with no calcification. There was also an inadvertent finding of an ill-defined enhancing lesion at the outer quadrant of the left breast measuring 1.3 cm × 2.9 cm × 1.8 cm (Figure 2) with multiple mediastinal adenopathies

in the prevascular space, right para-trachea, pre-trachea, sub-carina and right hilar, as well as evidence of bilateral pulmonary lymphatic infiltration. The largest lymph node was noted at the subcarinal, measuring 2.3 cm × 4.6 cm × 5.9 cm. Mammography was performed showing suspicious pleomorphic clusters of microcalcification at the center outer quadrant of the left breast (BIRADS 5) and an ultrasound-guided tru-cut biopsy showed extensive high nuclear grade ductal carcinoma in-situ (DCIS) (Figure 3) with comedonecrosis and dystrophic calcification (Figure 3A).

Various subspecialties were referred for multidisciplinary discussion, including infectious disease, haematology, respiratory, cardiothoracic, oncology, surgical and radiology. Due to lymphoma suspicion, the patient was advised to undergo an imaging-guided spleen nodule biopsy at another equipped tertiary facility, but she declined due to complication concerns. She was treated as advanced breast cancer with splenic lesion to rule out lymphoma or metastasis and mediastinal adenopathy. Consultation with oncologist is suggested for wide local excision/mastectomy.

A left mastectomy with axillary clearance was performed within 3 weeks with histopathological results revealing extensive DCIS of moderate to high nuclear grade with central comedonecrosis and microcalcification (Figure 3B). Only 1 out of 17 axillary lymph node was identified with evidence of metastasis. Hence, a diagnosis of multifocal invasive carcinoma of no special type with Nottingham's Histologic Score 7 (Grade 2) was made based on histopathological evidence, indicating malignancy with moderate differentiation. Based on tumour node metastasis staging system, a stage pT1b (>3) pN1a (AJCC 8th Edition) was given. Immunohistochemical analysis demonstrated the absence of oestrogen and progesterone receptors and the presence of HER2. Intravenous antibiotic was completed for 2 weeks, and she was discharged well a week post-operation.

Uncertainty of multiple mediastinal adenopathies and splenic lesion origin have hindered the commencement of adjuvant chemotherapy for breast cancer, as it could aggravate cytopenia if lymphoma was the underlying cause. Hence, endobronchial ultrasound biopsies were performed. However, the results were inconclusive, with only scanty blood seen. Eight weeks after mastectomy, she was admitted while awaiting consultation with the cardiothoracic team with complaints of right neck swelling, intermittent fever, and weight loss. On examination, a right cervical node was palpable measuring 2 cm × 3 cm. A tissue biopsy taken revealed diffuse and large malignant lymphoid cells with predominantly atypical centroblasts (Figure 3C) (homogenous CD20+, CD10+ (70%) and BCL6+ (90%)). There were numerous apoptotic bodies and tangible body macrophages, and the presence of proliferation index (Ki67) was 75% highly suggestive of a DLBCL. Following consultation with oncology, she was scheduled to receive doxorubicin and cyclophosphamide as adjuvant chemotherapy for breast cancer, which is also indirectly used to treat lymphoma.

Hence, the patient was then referred to a tertiary centre for lymphoma treatment with Rituximab–Cyclophosphamide–Doxorubicin–Vincristine–Prednisone (R-CHOP) regime. In between treatments, repeated computed tomography scans after the third cycle of chemotherapy showed a significant reduction in the size of cervical, mediastinal, and hilar nodes with smaller splenic lesions, indicating treatment response. Fluorodeoxyglucose-Positron emission tomography (FDG-PET) scan performed 8 weeks following the completion of chemotherapy showed no evidence of local, regional nodal or systemic metastasis. She has been keeping well since and is on regular monitoring.

DISCUSSION

The incidence of MPMs is rare but their prevalence has been increasing. According to Warren and Gates criteria, each tumour must be histopathologically confirmed, and distinct from each other, and the probability of one metastasising to another must be ruled out.[1] Guidelines issued by the International Agency for Research on Cancer (IARC) in 2004 suggested SMPMs could be used when the second primary cancer is detected within 6 months, whilst the term MMPMs are used whenever the second primary cancer is detected after 6 months from the first primary cancer being diagnosed.[2] The synchronous type is less common, accounting for about 30% of all MPMs.[5]

In a study by Lv et al.[6], it was observed that among 161 MPMs patients, 98 patients (60.9%) were male and the median age in the synchronous cancer group was 64 years old. In addition, adenocarcinomas (55.1%) and squamous cell carcinomas (23.1%) were the most commonly reported types of pathology, while sarcomas (1.3%) and haematological malignancies (6.4%) were among the least reported. The digestive (48.7%), urogenital (21.8%) and respiratory (15.4%) systems were the three leading systems in the synchronous tumour group. In contrast, our patient is a lady with primary tumours of the breast and haematological origin.

The exact pathophysiology of MPMs remains largely unknown.[5] Common risk factors may include inherited cancer predisposition, cancer-promoting aspects of lifestyle, hormonal and environmental factors, treatment for previous primary cancer and increased surveillance among cancer survivors.[5] Additionally, people with rheumatoid arthritis, such as our patient, were also found to have an increased risk of lung cancer and lymphoma than the overall population.[7] It was hypothesised that a long-term immunologic stimulation may increase the risk of malignant transformation of immune system cells (which may lead to clonal selection and predispose CD5+ B cells to malignant transformation), reduce the number of T-suppressor lymphocytes (including those directed against the pro-oncogenic Epstein–Barr virus) and inhibit the natural killer cell activity in the blood, synovial fluid, tissue and lymph, thus increasing the risk of lymphoma.[3] Although immune dysregulation is a feature of both malignancies and autoimmune diseases, the precise mechanisms underlying this susceptibility remain uncertain.

Woo et al.[8] found that the prevalence of synchronous breast cancer with non-Hodgkin's lymphoma (NHL) or a DLBCL was only at 29.7%. This indicates that the co-occurrence of breast malignancy and DLBCL is rare,[7] even though breast cancer may be diagnosed following treatment of Hodgkin's

lymphoma.[4] Our patient initially presented with constitutional symptoms, raised LDH, ESR and Ca-125, with significant imaging findings on the breast, spleen and mediastinal. It was possible that both breast cancer and lymphoma were present at the time, however, due to a lack of histopathological evidence to suggest lymphoma at the time, the diagnosis of breast cancer was established first. It was not until she presented again 2 months later with a right cervical lymphadenopathy, made an excisional biopsy possible to confirm the diagnosis of DLBCL. This was a point of a diagnostic quandary for us as an excisional biopsy to the mediastinal region and spleen was difficult to perform[9] when she first presented. Furthermore, obtaining a tissue biopsy from a difficult location requires invasive procedure and speciality that are not typically offered by many institutions.[10]

The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F- FDG PET/CT) is a new imaging modality that can distinguish between benign and malignant cells based on their higher uptake by tissues with increased glycolysis. PET scans, when combined with minimally invasive procedures in interventional radiology, can be useful in identifying additional primary malignancies. The clinician should strive to obtain histological diagnosis under such circumstances as misinterpretation of PET scan will be catastrophic as it might steer the direction of care towards palliation. Other modalities of molecular cytogenetics study such as fluorescence in-situ hybridisation (FISH) and the presence of BCL6 gene are highly associated with lymphoma. From a diagnostic standpoint, early detection and confirmation of such tumours are critical to determining the best treatment option for patients.

There is no universal protocol for treating synchronous multiple cancers. SMPMs treatment decisions should be individually tailored with a multidisciplinary approach. Consensus on therapeutic strategies should be adequately communicated to patients to ensure transparency and understanding. Our case had undergone a mastectomy following the diagnosis of DCIS, followed by chemotherapy after the diagnosis of DLBCL was established later. Prognostic factors for each type of tumour play an important role when deciding on treatment strategies. The possibility of a curative approach, the palliative situation, the degree of metastasis for each tumour, and the complications anticipated from anticancer therapy are significant points to consider when making clinical decisions.[2]

CONCLUSION

Despite the rarity, the incidence of MPMs appears to be on the rise. Therefore, physicians should be vigilant about the possibility of patients being at risk for new and separate cancers. MPMs may pose as diagnostic and therapeutic dilemmas. Hence, a thorough clinical and pathological staging of both malignancies, as well as interdisciplinary team discussions are required to determine the best management plan for the patients. Future research is warranted, particularly in the treatment of patients with synchronous or metachronous multiple primary cancers.

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