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Accelerated Chronic Lymphocytic Leukaemia Complicated by Bilateral Pathological Humeral Fractures

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A 77-year-old woman with a prior history of TP53-mutated chronic lymphocytic leukaemia (CLL) presented with a painful left arm. There was no history of trauma. The patient was on watch and wait after completing previous treatment with obinutuzumab-chlorambucil, ibrutinib and rituximab-venetoclax 5 years prior. X-ray of the left arm showed an acute

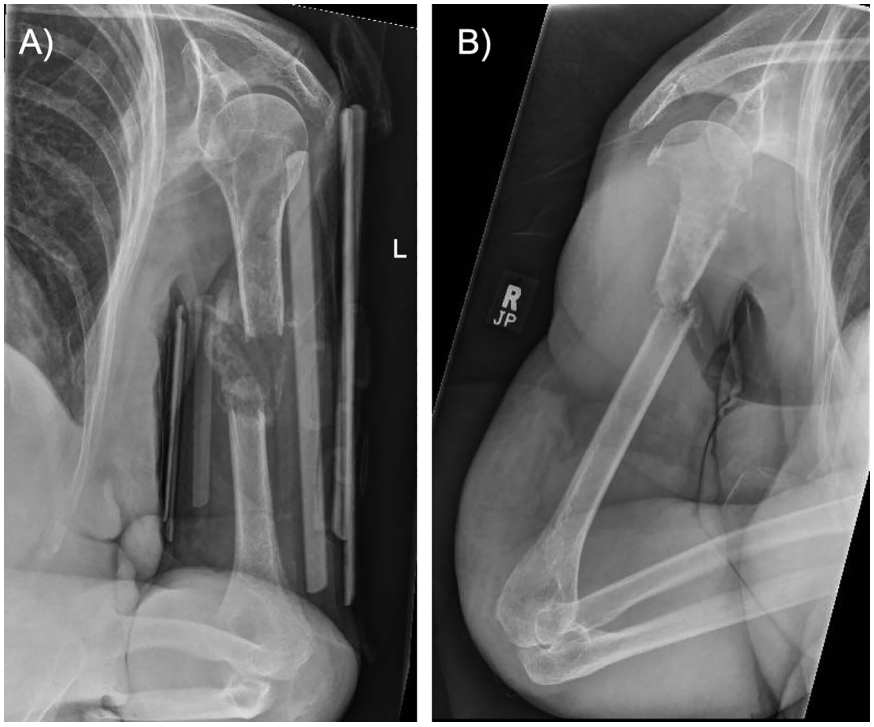

FIGURE 1 | Plain film x-rays demonstrating pathological humeral fractures. (A) Left humeral fracture; (B) right humeral fracture.

Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission

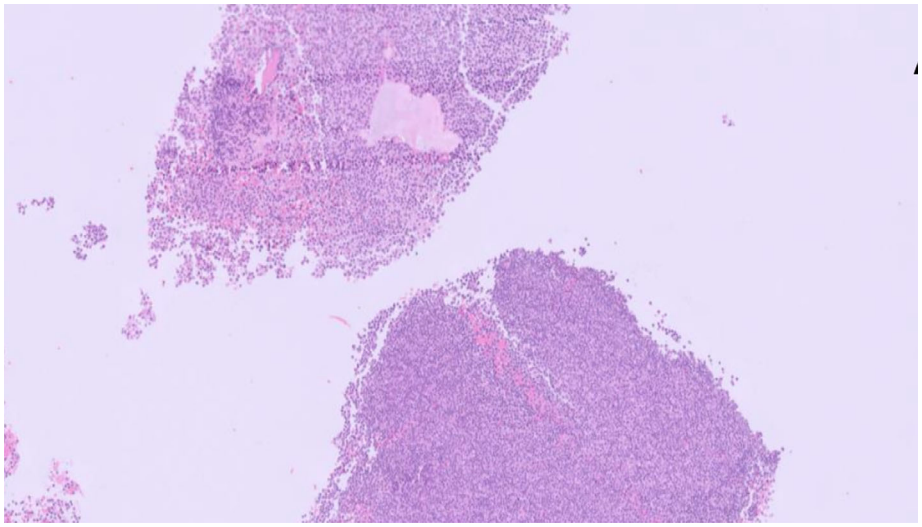

FIGURE 2 | Hematoxylin and eosin stain ×20. The humeral biopsy shows a proliferation of small lymphocytes with coarse chromatin. Interspersed with larger cells, including prolymphocytes and paraimmunoblasts, which constitute proliferation centres.

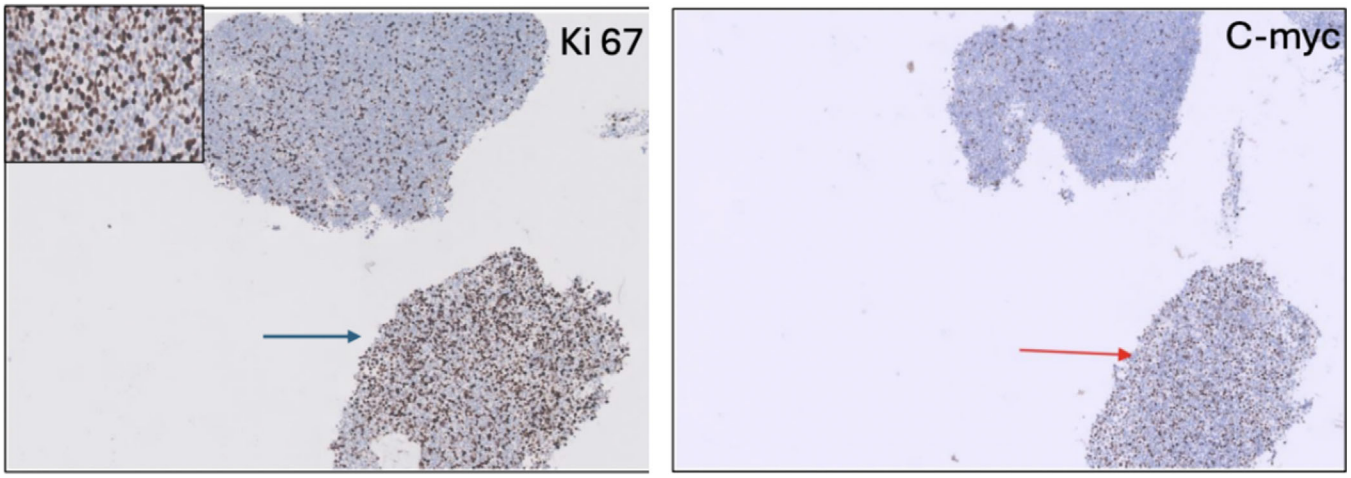

FIGURE 3 | Humeral biopsy. The Ki67 proliferation index is low in one of the fragments at ~10%, whereas elevated to more than 30% in the other (blue arrow and inset), which is a feature suggestive of histologically aggressive CLL/SLL (A-CLL). It is also coincides with variably increased C-Myc in the same fragment (red arrow).

proximal humeral fracture (Figure 1A). Physical examination did not demonstrate any palpable lymphadenopathy. Whole body CT demonstrated bilateral humeral bony infiltration and no nodal involvement. These findings were corroborated on PET-CT, with no other systemic disease. Working diagnosis at this point was Richter's transformation (RT) to diffuse large B-cell lymphoma (DLBCL). The Patient's lactate dehydrogenase (LDH) was raised at 350 U/L with normal calcium levels. Although a blood count was initially normal, she slowly developed peripheral lymphocytosis. Blood film revealed two populations of lymphocytes: one was small and mature, and the other was larger with nucleoli present.

During the investigation, the patient suffered another atraumatic fracture of the right arm, causing a significant functional decline (Figure 1B). Vitamin D levels were checked to screen for osteoporosis, which were normal. A bone marrow biopsy was not done as cell count was initially normal. CT-guided biopsy of the lytic lesion from the left humerus was done instead. This showed sheet-like proliferation of lymphoid cells. The cells were small and monotonous in appearance, but there was also a population of medium/large-sized cells with single prominent nucleoli likely to represent prolymphocytes (Figure 2). Neoplastic cells were immunopositive for cluster of differentiation (CD) 20, CD79a, CD5, CD23, LEF1 and BCL2. Ki67 proliferation index was variable across the cells; low (< 5%) in the areas of small lymphocytes but higher (30%–40%) in the areas of larger lymphocytes, which also coincided with variably increased c-myc expression (Figure 3). A diagnosis of accelerated CLL (A-CLL) was made. TP53 analysis showed a high allele frequency of > 85%.

Trials with novel agents were considered; however, the patient declined. As she was in remission for nearly 5 years since the treatment with venetoclax-rituximab, we re-treated her with venetoclax. Her humeral fractures were treated conservatively

alongside bisphosphonate therapy. Although she sustained a haematological response initially, she re-presented 3 months later with malignant hypercalcaemia and new liver deposits. The patient's performance status had also declined drastically and she became bedbound. The patient opted for palliative care and sadly died soon after.

This is an unusual case of A-CLL presenting with bilateral pathological fractures of humeri. A-CLL is rare and represents a transition state between CLL and RT. It is a histological variant of CLL with a frequency of less than 1% of all cases [1]. A-CLL remains a challenging diagnosis due to its overlapping features with RT, and due to the lack of radiological and laboratory markers which can conclusively identify A-CLL [1, 2]. A-CLL is associated with an aggressive clinical presentation and worse prognosis when compared to typical CLL [3]. Recent case studies have demonstrated the use of combinations of novel agents, including non-covalent BTK inhibitor in A-CLL with good patient outcomes [2].

Author Contributions

M.K., V.B. and J.D. wrote the paper. V.M. provided the histological diagnosis.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

Appropriate written consent was collected from the patient's next of kin.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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