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CASE REPORT

Chronic Lymphocytic Leukaemia and Multiple Myeloma

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ABSTRACT

Association of chronic lymphocytic leukaemia and multiple myeloma in the same individual is rare. These malignancies may be related through a common clonal origin, or exist as separate malignancies from different clones. Multiple myeloma may exist simultaneously with chronic lymphocytic leukaemia, or be diagnosed several months after chronic lymphocytic leukaemia. Common symptoms experienced in these rare cases are generally a combination of clinical features typically seen in chronic lymphocytic leukaemia and multiple myeloma separately. This report describes a 76-year-old man with coexisting chronic lymphocytic leukaemia and multiple myeloma. Diagnosis of chronic lymphocytic leukaemia preceded the diagnosis of multiple myeloma by approximately 4 years, and multiple myeloma presented with translocation t(11;14) that was not found in chronic lymphocytic leukaemia cells.

Key Words: *Bone marrow; Chromosome aberrations; Leukemia, lymphocytic, chronic, B-cell; Multiple myeloma*

中文摘要

慢性淋巴細胞白血病和多發性骨髓瘤

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慢性淋巴細胞白血病和多發性骨髓瘤很少會發生於同一個病例。這些惡性腫瘤可能經同源性克隆聯合發生，或作為源自不同克隆的惡性腫瘤而各自存在。多發性骨髓瘤可能和慢性淋巴細胞性白血病同時存在，也可能於慢性淋巴細胞白血病被診斷數個月後才發現。這些罕見病例的共同症狀為慢性淋巴細胞白血病及多發性骨髓瘤各自典型臨床特徵的綜合。本文報告一名同時患有這兩種病症的76歲男子，在發現多發性骨髓瘤的大約四年前，已診斷患有慢性淋巴細胞白血病。其多發性骨髓瘤帶有易位t（11;14）未有在慢性淋巴細胞白血病細胞中發現。

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INTRODUCTION

A patient treated in the Rapid Response Radiotherapy Program (RRRP) at Sunnybrook Health Sciences Centre, Ontario, Canada, had chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM). Association between these incurable B-cell malignancies is rare.[1,2] It is not known whether the two malignancies are always related, although they may arise from a common clonal origin.[2,3] Possible causes could be of clonal evolution, or an effect of previous CLL treatments, or plasma cell differentiation within a CLL population.[1,4] However, some patients, such as this one, shows findings consistent with two distinct clones. Symptoms typically present are presenting features of both CLL and MM. Stage-dependent anaemia and immune deficiency are features commonly present in these diseases.[3,5]

CASE REPORT

In November 2012, a 76-year-old man with biopsy-proven CLL and MM was referred to the RRRP for palliative radiotherapy. He had been diagnosed with CLL in January 2009, and subsequently diagnosed with MM in November 2012. At the time of diagnosis of CLL, the patient underwent chemotherapy after positive a bone marrow biopsy of the iliac spine for B-CLL, with more than 80% marrow involvement. The aspirate showed diffuse replacement by small lymphocytic cells. The patient presented again in 2012 with multiple bone lesions, impending fracture, diffuse osteopenia of the bones and anaemia, with no lymphadenopathy. He also had severe pain in one rib, and had previously required orthopaedic intervention for multiple compression fractures of the spine. Bone marrow aspiration was taken from the T11 compression fracture in 2012 when the patient underwent orthopaedic intervention. This demonstrated lymphocytes that were plasmacytoid, leading to differential diagnoses of cyclin D1 (+) CLL with concurrent Mantle cell lymphoma, plasma cell dyscasia, or lymphoplasmacytic lymphoma. The clinical manifestation of MM occurred almost 4 years after the patient had been diagnosed with CLL. Lesions in the proximal left femur and distal right humerus were consistent with myeloma.

Blood tests and bone marrow biopsy determined that the lymphocytes and plasma cells expressed immune phenotypes associated with both CLL and MM, respectively (Figure 1). Malignant infiltrate was confirmed through a biopsy of the rib cage in 2012, and the infiltration level was approximately 80% of the bone marrow cells. The bone marrow smear showed an elevated number of small plasma cells (33%), and lymphocytosis, with small lymphoid cells comprising 22% of cells (Figure 2).

The patient received radiation treatment to the left femur (30 Gy in 10 fractions) and to the painful left rib (8 Gy in 1 fraction) in December 2012. Preceding treatment, the large 3.9-cm lytic lesion in the left femur had been asymptomatic. Following treatment, imaging showed no improvement in the size of the lesion. Consequently, this still presented a risk of fracture. There was also an incomplete response to radiation treatment of the rib, and it remained painful. In January 2013, the patient started palliative chemotherapy and is still alive at the time of writing this report.

DISCUSSION

CLL is defined as a heterogeneous disease of continuing accumulation of abnormal lymphocytes. A diverse range of genetic abnormalities can affect the outcome of CLL in patients, which is variable.[6] As a result, the prognosis may be very poor for some patients due to aggressive disease. Conversely, the disease may take on a more prolonged course.[7] Treatment may be more aggressive for patients with good performance status, such as the use of a combination of fludarabine and cyclophosphamide with rituximab, a biological therapy.[8] In contrast, a gentle approach may be adopted for patients with poor performance status, such as chlorambucil therapy. Brouet et al[3] found that, in a cohort of 11 patients, most were treated with chlorambucil initially.

MM is an accumulation of abnormal and rapidly proliferating mature plasma cells within the bone marrow.[2,3,9] This can be treated by chemotherapy or by novel agents with or without chemotherapy, followed by stem cell transplantation. A commonly used chemotherapy regimen in the past was a doublet containing melphalan-prednisone.[2,8]

The prognosis of CLL and MM varies depending on factors such as the stage of disease or susceptibility to treatment. Chemotherapy is the most common method of treating the co-occurrence of CLL and MM.[3,4]

There is an increasing number of reports of these two associated malignancies. Accompanying this is an increase in the possibility of a relationship between CLL and MM, and how their cause could be related.

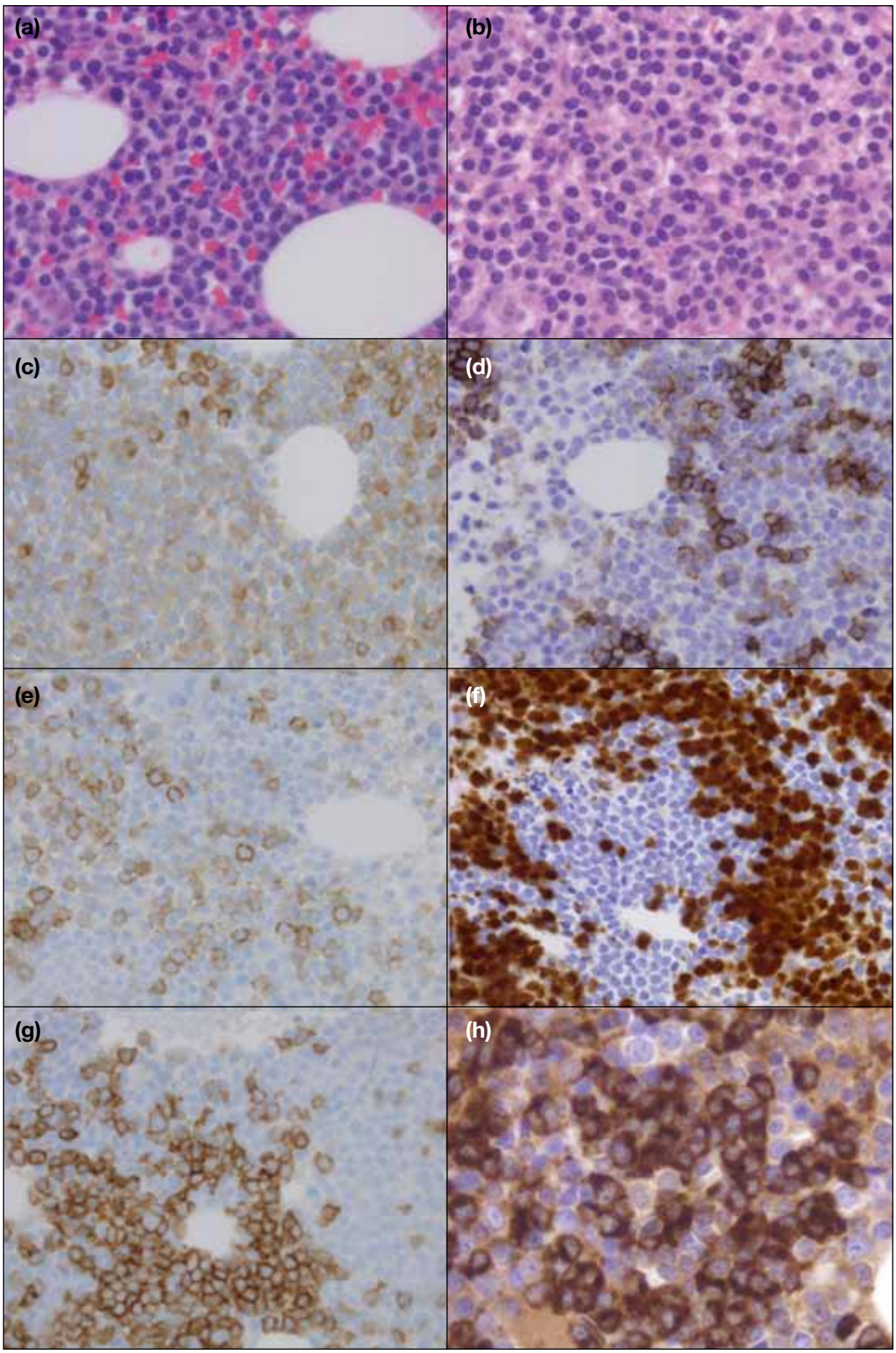

Figure 1. Chronic lymphocytic leukaemia (CLL) infiltrates are illustrated in the left panels and plasma cell myeloma in the right panels. Bone marrow clot sections show areas with infiltrates composed of (a) mainly small lymphoid cells corresponding to B-CLL and (b) mainly small plasma cells (H&E, original magnification, x 40). (c) shows CD79a immunostaining that is weakly positive in CLL cells and strongly positive in plasma cells (original magnification, x 40). Plasma cells are positive for (d) CD138 and (f) cyclin D1, and (h) show monotypic kappa expression (original magnification, x 63). B-CLL cells show characteristic phenotype with positivity for (e) CD23 and (g) CD5 (original magnification, x 40). CD20 was negative in both populations (not shown).

The possibilities are that the two malignancies derive from either distinct or common clonal origins.[2,10] In this patient, CLL and MM were most likely to be two distinct malignancies. Although both diseases are kappa+, the CLL cells were negative for cyclin D1 expression, indicating the absence of t(11;14) that was demonstrated in the MM cells by fluorescence in-situ hybridisation (Figure 3). Taken together the results are consistent with two different clones.

In another report, it was determined that both CLL and MM were derived from a single clone, mainly from examining immunoglobulin G (IgG) and IgA antibodies synthesised by CLL and malignant plasma cells. The B-CLL cells were found to represent predecessors of IgA plasma cells, suggesting another rare link between CLL and myeloma.[10] Saltman et al[2] reported a similar finding in 1989, outlining supplemental evidence of CLL and MM associated by a single clonal origin. In that report, a 52-year-old man was diagnosed with concomitant CLL and MM. It was determined through investigation into heavy chain genes that both diseases originated from a common B-cell clonal origin.[2] Co-existence of two separate malignancies, which was likely in this patient, was reported by Hoffmann and Rudders.[11] The discovery of MM in a 68-year-old patient was similar to this patient, in that both patients experienced back pain and had an enlarged spleen while having asymptomatic CLL. However, the patient in Hoffmann and Rudders' report progressed rapidly despite chemotherapy and radiation therapy, experienced lytic lesions and compression fractures of the bone and, shortly thereafter, death.[8,11]

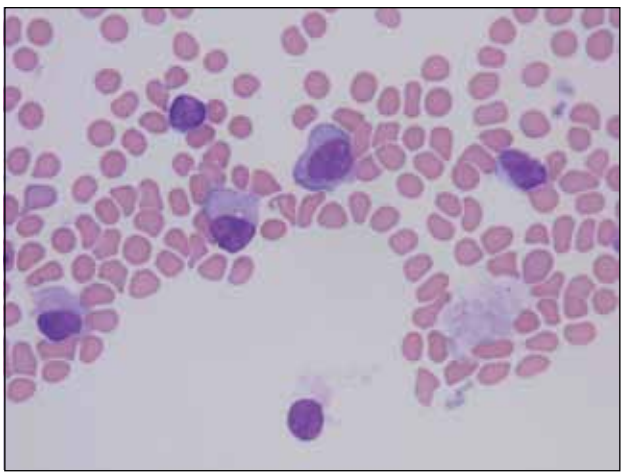

Figure 2. Bone marrow smear shows 33% plasma cells and 22% small lymphoid cells (May-Grunwald-Giemsa stain; original magnification, x 63).

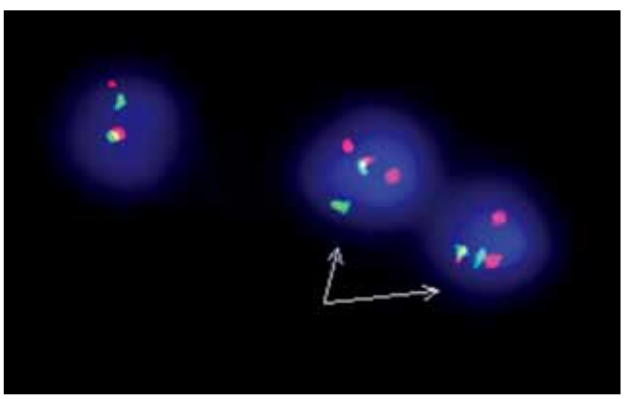

Figure 3. Interphase fluorescence in-situ hybridisation study of the bone marrow aspirate in 2012 shows the abnormal juxtaposition of the immunoglobulin heavy chain (green) and cyclin D1 (red) genes. This pattern was seen in 36.5% of nuclei, corresponding to the cyclin D1–expressing multiple myeloma population.

Frequently, CLL and MM are reported simultaneously or CLL precedes MM, and only rarely does CLL present after MM.[8] In 1985, it was shown that 20 of 35 reported patients were diagnosed with MM 2 to 15 years after the diagnosis of CLL.[3] In one 76-year-old patient with symptoms of back pain and lymphocytosis, both malignancies occurred simultaneously.[3] Very few reports of MM preceding CLL have been found.[3,6,12] However, this may be due to the time of diagnosis relative to the appearance of clinical manifestations. Zalcberg et al[12] documented a rare case of MM preceding CLL, in which a common clinical feature was seen as skeletal disease, with associated relapse in an extraosseous site.[12] Almost 3 years later, the patient was diagnosed with CLL, and the malignancies were determined to have separate clonal origins.[6,12] Extraosseous lesions were also found to occur in six of 33 patients in a review by Brouet et al.[3]

A report in 1985 documented a 61-year-old woman primarily diagnosed with CLL.[10] Approximately 12 years later she was found to also have MM.[10] MM was only found because of the appearance of lytic lesions throughout the skeleton, leading to pathological fractures and bone pain.[10] Appearance of osteolytic disease of the bones, hypercalcaemia, and elevated serum Ig are common clinical outcomes of the two diseases.[13] Of 11 cases reviewed by Brouet et al,[3] the feature of osteopenia was a frequent presentation. A common clinical feature of osteolytic lesions that

appeared in this patient also occurred in most of the patients investigated by Brouet et al,[3] with six of 11 patients presenting with skeletal lytic lesions. These lesions developed at variable times, occasionally leading to discovery of a malignancy, or were an indication of disease progression.[3] In the report by Fermand et al,[10] lytic lesions developed shortly after MM was diagnosed. In this patient, bone pain, lytic lesions, and multiple pathological fractures ultimately led to the diagnosis of MM.

There is still an absence of information about these rare cases, and continuation of documented cases may facilitate more research and knowledge about this rare entity. Further research should investigate whether there are differences in clinical progression of disease between patients with CLL and MM from the same or different clones. Additional knowledge may guide physicians in the optimal treatment strategies and clinical markers would help to confirm the presence of these malignancies.

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