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Hodgkin's lymphoma as a second cancer in multiple myeloma never exposed to lenalidomide

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Dear Editor,

A 54-year-old man, with good past health, was diagnosed to have International Stage III, IgG myeloma in Dec, 2006 with IgG M-protein measuring 116g/L, serum albumin 22g/L (normal: 40-50g/L) β_2 -microglobulin of 9.25 mol/L and 56% plasma cell infiltration of the bone marrow at diagnosis. He achieved a partial remission with a 83% reduction of M-protein to 15g/L after the induction with the staged approach, [1,2] which comprised three cycles of VAD (vincristine, adriamycin and dexamethasone), followed by 4 cycles of salvage VTD (bortezomib, thalidomide and dexamethasone) in patients failing a $\geq 75\%$ reduction in M-protein level after VAD. He achieved very good partial response (VGPR, i.e. $>90\%$ reduction of M-protein), and immunofixation-negative complete remission (CR) at 3 and 6 months after autologous stem cell transplantation (ASCT) in July, 2007. He was entirely asymptomatic until May 2012 when he complained of a painless left cervical lymph node. Excisional lymph node biopsy showed enlarged lymph node with effaced nodal architecture, which was replaced by a mixed inflammatory infiltrate with scattered large-sized classical Reed-Sternberg cells. (Figure 1A, hematoxylin and eosin, x 200) The Reed-Sternberg cells were positive for Epstein-Barr encoded early RNA (EBER), (Figure 1B, x 200) and expressed CD30, (Figure 1C, x 400) and CD15 (Figure 1D, x 400). Finally, clonality study by polymerase chain reaction for immunoglobulin heavy chain (IgH) gene showed clonal IgH gene rearrangement in the diagnostic myeloma (MM) but not Hodgkin's lymphoma (HL) sample. (Figure 2). Therefore, the overall features were consistent with mixed cellularity classical Hodgkin's lymphoma (HL) with no evidence of plasma cell neoplasm.

Staging combined positron-emission tomography-computed tomography (PET-CT) scan showed generalized lymphadenopathy in cervical, mediastinal, abdominal and pelvic regions with maximum standardized uptake value (SUVmax) ranging from 3.8 to 15.5. Bilateral trephine biopsies revealed no plasma cells or lymphoma infiltration. Therefore, this patient had Ann Arbor Stage IIIA Classical HL during CR of myeloma. He was planned for 6 cycles of ABVD. Interim PET-CT assessment showed CR after 3 cycles of ABVD.

Myeloma is a neoplastic proliferation of mature, post-germinal center B-lymphocytes. Recent combination of novel agents induction followed by ASCT has markedly improved CR rates and survivals. The advent of the staged approach aimed to reduce the expensive use of bortezomib upfront while preserving CR rate. [1,2] Second primary malignancies (SPM) have been reported in myeloma, in particular in the setting of ASCT, after which therapy-related myelodysplastic syndrome or therapy-related acute myeloid leukemia may occur after high-dose melphalan.

Recently, SPM including lymphoid malignancies have been reported in transplant-eligible myeloma patients receiving lenalidomide maintenance therapy. [3,4] In the French study, 26 SPM occurred in the lenalidomide maintenance arm compared with 11 SPM in the placebo arm ($p=0.002$). [3] Of these, 13 were hematological cancers, which comprised MDS/AML (N=5), ALL (N=3), NHL (N=1) and HL (N=4). [3] Similarly, an increased risk of SPM including hematological cancers of lymphoid origin, with ALL (N=5) and HL (N=1) compared with absence of these lymphoid malignancies in the placebo group, [4] has also been shown in another trial in which transplant-eligible myeloma patients were randomized to receive lenalidomide or placebo. Moreover, in a large series of 589 consecutive myeloma patients between 1997 and 2008, [5] thirteen patients developed a hematological malignancy. Apart from 6 cases of

MDS/AML, which occurred at more than 50 months after the diagnosis of myeloma, one patient had concomitant HL with myeloma. Therefore, sequential Hodgkin's lymphoma in myeloma may occur even in the absence of prior treatment with lenalidomide.

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Legend

Figure 1. Excisional lymph node biopsy showed enlarged lymph node with effaced nodal architecture, which was replaced by a mixed inflammatory infiltrate with scattered large-sized classical Reed-Sternberg cells with large-sized, mirror-image vesicular nuclei and prominent eosinophilic nucleoli in addition to Reed-Sternberg cell variants. (Figure 1A, hematoxylin and eosin, x 200) In-situ hybridization for Epstein-Barr encoded early RNA (EBER) showed that the Reed-Sternberg cells were positive. (Figure 1B, x 200) Immunohistochemical stains showed that the Reed-Sternberg cells were positive for CD30, (Figure 1C, x 400) with a proportion positive for CD15 (Figure 1D, x 400)

Figure 2. Polymerase chain reaction for immunoglobulin heavy chain (IgH) gene showed clonal IgH gene rearrangement in the diagnostic myeloma (MM) in addition to the positive control (P) but not Hodgkin's lymphoma (HL) sample, negative control or reagent blank. (Figure 2A). In addition, positive PCR for β -hemoglobin confirmed integrity of DNA samples (Figure 2B)