Synchronous dual hematological malignancies: new or underreported entity?

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**ABSTRACT**

**Background:** Patients with a single hematological malignancy may be unexpectedly diagnosed with a clonally unrelated synchronous dual hematological malignancy (SDHM). The presence of a secondary hematological malignancy may be overlooked and only identified in situations presenting with discordant clinical or laboratory findings. Clinical management of these patients can be challenging, in part due to the relatively unknown etiopathology of SDHM and the impact of therapy on the secondary malignancy.

**Objectives:** To assess, characterize patients with synchronous double hematological malignancies and share our experience with this challenging group of patients.

**Methods:** We performed a retrospective chart review of 3036 patients with hematological malignancy at our cancer center between February 2013 and July 2017.

**Results and discussion:** We identified 46 patients with SDHM, a prevalence of 1.51% among patients diagnosed with any hematological malignancy. We identify several heterogeneous combinations of SDHM comprised of myeloid and/or lymphoid lineages and provide our experience with managing patients with these underreported conditions.

**Conclusion:** SDHMs are not uncommon and should be suspected in situations presenting with unusual or unexpected findings.

**KEYWORDS**
synchronous dual hematological malignancy; lymphoid; myeloid

**Introduction**

Over the past few years, we have observed an increasing number of patients referred to our cancer center with a single hematological malignancy (SHM) who were unexpectedly diagnosed with a synchronous dual hematological malignancy (SDHM), either incidentally during routine clinical work-up or because of discordant clinical/laboratory findings. Concurrent secondary malignancies may be masked by the primary malignancy and it is likely that patients with SDHM are underdiagnosed/underreported. Indeed, there are only rare reports of dual hematological malignancies in the literature [1–4], with practice guidelines to assist with diagnosing, treating, and monitoring patients lacking. As such, the management of these patients is challenging and may differ from SHM. The impact of comorbidity on disease progression and treatment outcomes remains unknown.

**Methods**

We performed a retrospective chart review of 3036 patients with hematological malignancy at our cancer center between February 2013 and July 2017. We identified SDHM patients using the following inclusion criteria: (i) clinical and pathological confirmation of dual hematological malignancies based on World Health Organization 2008 criteria [5] (ii) both malignancies were clonally unrelated; (iii) secondary primary malignancy was diagnosed/presented within 4 weeks of the first primary malignancy. We excluded patients with: (i) closely related diseases (lymphoproliferative disorders (LPDs) with bone concordant marrow involvement, paraprotein), since it represents different sites of involvement by the same single LPD; (ii) transformed disease (multiple myeloma (MM) from smoldering MM, monoclonal gammopathy of uncertain significance (MGUS), aggressive histology LPD with background of low-grade LPD, Richter’s transformation). The study was approved by the hospital’s research ethics board.

**Results and Discussion**

We identified 46 patients with SDHM, a prevalence of 1.51% among patients diagnosed with any hematological malignancy. The median age at primary diagnosis was 74 years (range 23–95), with a male predominance (65%). The majority of patients (96%) were diagnosed with SDHM at our institution, two by an off-site hematologist. All patients except one were Caucasian. Referrals from general practitioners were it is general hematological diagnosis (e.g. lymphoma, anemia) in 65% of cases, with nonspecific symptoms for the remaining cases. Referrals from specialists were more accurate, with only asymptomatic secondary diagnoses

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missed. In all cases, the discovery of a concurrent secondary malignancy was unexpected.

Three types of SDHMs were identified (Table 1): (i) myeloid + lymphoid (50%); (ii) lymphoid + lymphoid (43%); (iii) myeloid + myeloid (7%). Fourteen SDHM patients (30%) had at least one concomitant nonhematological cancer (cutaneous or solid); the majority of which were in the lymphoid + lymphoid group (64%). Thirty-three patients (72%) required therapy for the primary malignancy, 13 patients (29%) were on active surveillance. By the data cutoff date, 40 patients (87%) required initiation of therapy for the primary or secondary malignancy; three patients (13%) showed disease progression. Of these, 37 patients (80.4%) were alive, 9 patients (19.6%) had died, 6 from disease progression and 3 from unrelated health issues.

Myeloid + lymphoid

The majority of SDHMs were myeloid + lymphoid, with a prevalence of 0.75%. The median age was 71 years (range 51–95), with male predominance (74%). The most frequent diagnoses were a combination of either myeloproliferative neoplasm (MPN) + MGUS or myelodysplastic syndrome (MDS) + other malignancy (43.5%). Chronic lymphatic leukemia/small lymphatic lymphoma (CLL/SLL) was the most common concomitant lymphoid malignancy. Twenty patients (87%) required initiation of therapy for primary or secondary malignancy; three patients (13%) were on active surveillance. By the data cutoff date, 17 patients (74%) were either in remission or had stable disease; six patients (26%) progressed. Two patients (8.7%) who were in remission died from unrelated causes.

Our management experience of myeloid + lymphoid SDHM was as such: (i) MPN/MDS course was not influenced by LPD; (ii) azacytidine resulted in decrease of T-cell large granular lymphocyte clone; (iii) a phlebotomized Polycythemia Vera patient developed profound anemia on R-CHOP chemotherapy, requiring transfusions and erythropoetin administration; (iv) hydroxyurea (>1000 mg/day) decreased level of M-protein in all subtypes of MGUS; (v) treatment with bendamustine/rituximab required intensive transfusion and growth factors support for LPD patients with concomitant MDS; (vi) Ruxolitinib precipitated lymphocytosis in concomitant CLL/SLL, similar to Bruton’s tyrosine kinase inhibitors as described by Spaner et al. [6].

The coexistence of CLL/MBL and MPN is the most commonly described dual hematological malignancy to date. A retrospective review GINEMA analysis identified 46 such patients, an overall incidence of 1%, but synchronous CLL + MPN was found in 7 patients (18.5%). Distribution of MPNs was similar to asynchronous CLL + MPN. Treatment with hydroxyurea and Ibrutinib did not affect CLL. MPN course was not influenced by CLL, and concomitant CLL was indolent with good prognostic features [7]. A recent publication presented 13 CLL + MPN patients, however, only one had synchronous CLL + myelofibrosis [8].

Lymphoid + lymphoid

The prevalence of patients with lymphoid + lymphoid SDHM was 0.66%. The median age was 76 years
bone marrow was well described recently [4]. Concordantly, lymph node biopsy and secondary lymphoma in a single anatomic organ/tissue [9], including HL, B- or T-cell lymphoma (CL; 20%), and discordant bone marrow involvement (DBMI; 20%). A combination of a lymphoma with plasma cell dyscrasia (MGUS/MM/amyloidosis) was the most common (20%). The lymphoid + lymphoid group had the highest frequency of concomitant nonhematological cancers (64%). Eleven patients (55%) required therapy, nine (45%) were on active surveillance. By the data cutoff date, 19 patients (95%) were in clinical remission or had stable disease; one (5%) have progressed and died from MM. One patient in complete remission died from unrelated issues. The majority of secondary lymphoid cancers (95%) were indolent and required active surveillance only. One patient with follicular lymphoma completed nine cycles of melphalan/prednisone/bortezomib for MM, resulting in complete resolution of lymphadenopathy. When lymphoid + lymphoid SDHMs required therapy, we targeted the more aggressive primary or secondary malignancy. We used R-CHOP for diffuse large B-cell lymphoma + Hodgkin’s Lymphoma (HL), and R-CHOP + etoposide for Angiomyeloblastic T-cell lymphoma + DBLCL. Adriamycin/bleomycin/vinblastine/dacarbazine for HL completely resolved cutaneous T-cell lymphoma lesions.

Available literature describes CL as a coexistence of two distinct types of lymphoid neoplasms occurring in a single anatomic organ/tissue [9], including HL, B- or T-cell non-Hodgkin lymphoma [10]. Incidence of CL varies from 1% to 4.7% [11] and CL poses a particular diagnostic challenge with no agreed standards for treatment [12]. DBMI with DLBCL diagnosed on lymph node biopsy and secondary lymphoma in the bone marrow was well described recently [4]. Concordant BMI with DLBCL portends a worse outcome, in contrast to a discordant BMI with an indolent B-cell lymphoma. We had 3 patients with the same lymphoma pattern and 1 with both indolent lymphomas. In all cases, the presence of second lymphoma in bone marrow did not require therapy.

Myeloid + myeloid

We had only 3 myeloid + myeloid SDHM patients: one with concomitant acute myeloid leukemia + myelofibrosis. This patient was referred initially with iron-deficient anemia due to GI bleed. There was neither previous history nor symptoms of myelofibrosis. Another patient had primary mast cell leukemia (pMCL) and chronic myelomonocytic leukemia (CMML). Though association of pMCL and CMML is not described, systemic mastocytosis with associated clonal hematological nonmast-cell lineage disease is a known WHO-defined category. However, clinical course of each malignancy was markedly different, requiring cladribine for pMCL and azacytidine for CMML. Yet, the place of myeloid + myeloid combinations as true SDHMs needs to be clarified.

Conclusion

SDHMs are not uncommon and should be suspected in situations presenting with unusual or unexpected findings. The high frequency of concomitant solid tumors amongst SDHM patients suggests increased susceptibility or impaired immunity. The majority of SDHM can be managed expectantly. If both malignancies require treatment, the therapy should be targeted to the more aggressive malignancy. While we acknowledge that our recommendations are limited by the small sample size, we aim to raise greater awareness about SDHMs and encourage greater research in this area. In time, we hope to provide more comprehensive clinical information for SDHM patients and suggest that other health care providers share their experiences with this unusual and underreported patient population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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