CASE REPORT

Small lymphocytic lymphoma with Reed Sternberg cells: a diagnostic dilemma

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SUMMARY

Reed Sternberg (RS) cells in the setting of small lymphocytic lymphoma (SLL) can complicate the histopathological diagnosis. We report a case of a man aged 54 years who presented with cervical lymphadenopathy. Resection of the lymph node was performed and sent for histopathological evaluation to a local laboratory. A diagnosis of SLL with Classic Hodgkin's lymphoma (CHL) was made. The medical oncologist who encountered this diagnosis for the first time sent the biopsy blocks to our laboratory for a second opinion. On review of the biopsy and immunohistochemical stains, it showed typical SLL morphology and immunophenotype. Focally, it showed large mononuclear RS type cells; however, no typical background of CHL was seen. The diagnosis was revised to 'SLL with RS like cells with no convincing evidence of CHL'. The patient was subsequently treated as a case of SLL and no progression was observed on a follow-up of 5 years.

BACKGROUND

There is evidence to suggest that Hodgkin's lymphoma (HL) should not be diagnosed in the setting of small lymphocytic lymphoma (SLL) on the basis of Reed Sternberg (RS) cells only. Although controversial, the classic background of HL, characterised by RS cells found admixed with accessory and non-tumourous inflammatory cells, should also be present for establishing a diagnosis.¹ These two different scenarios, that is, SLL with HL transformation and SLL with only a few RS type cells, ascertains that pathologists should be aware of the two possibilities to avoid misdiagnosis. The prognosis between SLL cases and SLL with Hodgkin's transformation differs markedly;² however, it is unclear if there is a significant difference in survival between cases of SLL with few RS cells without a classic HL background and SLL cases with HL.

CASE PRESENTATION

A man aged 54 years presented to the clinic with cervical lymphadenopathy in the year 2012. Other symptoms included fever and generalised weakness. There was no significant weight loss. His medical history was unremarkable. On examination, there was lymphadenopathy but no hepatosplenomegaly. Haematological work up was negative.

INVESTIGATIONS

Lymph node resection was performed and sent for histopathological evaluation.

The following morphologic features were observed on H&E: typical SLL morphology, few large mononuclear RS type cells seen focally without appropriate background of T cells, histiocytes, eosinophils, neutrophils and plasma cells. (figure 1A, B), Immunohistochemistry analysis showed: (figures 1 and 2C–I): CD20+, CD3–, CD5+, CD23+, Cyclin D– and low Ki-67. The large mononuclear RS type cells were CD30+, CD15+, CD20+, LMP1+, PAX5+.

DIFFERENTIAL DIAGNOSIS

1. SLL with classic Hodgkin's lymphoma (CHL)
2. SLL with RS type cells

TREATMENT

Three cycles of rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP) with radiation were given.

OUTCOME AND FOLLOW-UP

The patient has been in remission since the past 5 years and is under follow-up.

DISCUSSION

SLL is a common low-grade B-cell lymphoma.¹ Approximately 2–8% of the patients with SLL may develop a more aggressive diffuse large B-cell lymphoma, which has a dismal prognosis. At the other extreme, <1% of the cases of SLL may also transform into Hodgkin's lymphoma (HL) with the characteristic RS cells.³ Besides Hodgkin's transformation of SLL, a few cases may also show the presence of scattered RS type cells without the appropriate background typically seen in HL. A recent publication described two such cases.⁴ These cells may or may not be EBV-positive.⁵ All neoplasms have two components: actual tumour cells and their microenvironment. Both are considered essential for the progression of the tumour. In HL, this phenomenon is at its extreme, such that the neoplastic cells represent only 0.1–1% of the cell population while the tumour microenvironment makes up the remaining cellular infiltrate.¹

To unravel the mystery behind the origin of RS cells in SLL, a number of studies have been conducted. A research in 1998 proposed that RS cells in SLL originated from the same B cell clone. Their investigation used IgH CDRIII sequences in RS and SLL cells to map their genesis, and two out of three were found to share a common origin.⁶ Another study unveiled a novel mechanism, unfolding the process by which B cells in the germinal centre underwent somatic hypermutations giving

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Figure 1 (A and B) H&E, (C) CD20 and (D) CD3.

Figure 2 (A) CD5, (B) CD30, (C) CD15, (D) LMP1 and (E) CD23.

rise to SLL cells and RS cells. This study suggested that the RS cells in SLL emerged from the germinal centre B cells, either from the same clone that created the SLL cells or as distinct clones of B cells transformed from EBV infection.⁵ EBV LMP-1 testing identified the presence of this virus. ZAP-70 staining has been used by some researchers to elucidate RS cells arising from mutations in SLL cells. This marker was negative in cases where RS cells were clonally related to SLL cells and positive in others which were unrelated and emerged spontaneously.⁷ Other mechanisms thought to play an instrumental role include immunosuppression, an important component of SLL, which sets the stage for the development of other malignancies, including HL.^{8–9} It is still not clear if the HRS cells in SLL are a potential precursor for Hodgkin's transformation.

It is pertinent to be aware that, strictly speaking, CHL is also a B-cell lymphoma, however since B-cell differentiation programming is incomplete in CHL, it usually does not express classic B-cell antigens like CD20 and CD79, albeit positive at times in up to 20% of the cases. The same is the rationale for the so-called dim Pax5 positivity in HL compared with bright positivity in other B-cell lymphomas. This cross-reactivity indeed poses significant diagnostic problems so much so that in 2008 the WHO lymphoma classification, a category of 'B-cell lymphoma, unclassifiable with features intermediate between diffuse large B-cell lymphoma and Classic Hodgkin Lymphoma', was included. This immunophenotypic overlap is typically and particularly common in 'Primary mediastinal large B-cells lymphoma' and its distinction from CHL at this site may be highly challenging.¹⁰ In the updated WHO classification this category is renamed as 'Grey zone between CHL and large B-cell lymphoma'. In addition, secondary Hodgkin-like blasts presence in other B-cell lymphomas like CLL and FL is emphasised.¹¹

In this case report, we have presented a case of SLL with scattered RS cells, without a typical background of CHL. In 2008, the WHO classification of lymphoid tumours recommended that to make a diagnosis of CHL in the setting of CLL/SLL, presence of few RS cells is not enough, rather RS cells along with a classic background of HL is required.¹ However, at this point in time, it is unclear if the two morphological types have biological and clinically significant differences. In a recent study published in 2016,⁷ the authors evaluated the differences between the two types. In this study, cases with SLL/CLL with a few RS cells similar to ours were labelled as type 1, whereas type 2 included those cases with typical HL morphology in the setting of SLL/CLL. The study compared 26 cases of type 1 with 51 cases of type 2 in terms of prognosis, clonality and EBV status. This is the largest study until now that aimed at investigating the differences between the two types. The authors concluded that there was no difference between survival and prognosis between the two distinct morphological types. Advanced age rather than morphology was identified as a factor for poor prognosis. The morphology or EBV status did not affect the clonality of RS cells. In type 1 and type 2 morphology, the RS cells were found to be clonally related to CLL cells in some cases, while in several other cases, they had a distinct origin. Also, there was no difference in the immunophenotype or EBV status of RS cells in both types. Another important conclusion was that type 1 morphology might be an initial stage that later may progress to type 2.

To summarise, there are two morphologically separate scenarios of SLL/CLL containing RS cells. Though there are multiple

results in the literature, the largest study shows that both types carry a similar clinical risk.⁷ Further studies are needed to understand the complete significance of RS cells in SLL without the classic background.

Learning points

- ▶ The quite uncommon yet distinct histological variant of small lymphocytic lymphoma (SLL) with Reed-Sternberg (RS) cells has been delineated. The cells in this subtype show the classic morphology and immune phenotype of RS cells; however, the typical microenvironment of classic Hodgkin's lymphoma is absent.
- ▶ The RS cells may or may not be clonally related to the SLL cells. Infection with EBV may also be an important trigger for the formation of HRS cells in SLL, as indicated by EBV-LMP1 immunohistochemical testing.
- ▶ The two morphological variants of SLL with RS cells pose a diagnostic dilemma for pathologists. They can complicate the diagnosis of SLL in either the bone marrow or lymph node biopsies.

Contributors The corresponding author diagnosed and identified the case. BA and HS searched the literature and wrote the manuscript under the guidance of the corresponding author.

Competing interests None declared.

Patient consent Obtained.

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