

Type of Article: REVIEW**Splenic Micronodular T-cell/Histiocyte-Rich Large B-cell Lymphoma: The Corticosteroid Pretreatment Hypothesis**

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Abstract

Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma is possibly derived from nodal T-cell/histiocyte-rich large B-cell lymphoma; however, a transition between the nodal and splenic micronodular forms has not been described to date. Of note, the only lymph nodes to be involved in association with the splenic micronodular pattern of the disease are the splenic hilar lymph nodes, and that, with partial involvement only. Kan et al, in their series of articles, have raised the possibility that corticosteroids, when prescribed prior to splenectomy, cause histopathological and functional modulations (apoptosis, necrosis, tissue shrinkage), which

modify or even obscure the diagnostic morphological features. The indications for glucocorticoid therapy are either related to the suspected lymphoma, or else to other comorbidities, like asthma and autoimmune disorders. We propose that patients with the splenic, rather than nodal subset of the disease are likely to have been prescribed corticosteroids prior to histopathologic examination of the involved tissue, causing disparate morphologies in the spleen. Apoptosis, as induced by corticosteroids, is hypothesized as the major mechanism initiating the histopathological and functional changes in the splenic micronodular variant of our patients.

Keywords: splenic micronodular B-cell lymphoma; corticosteroids; apoptosis; shrinkage

Introduction

Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma (MTLBL) is a rarely diagnosed entity [1]. This variant, considered by many as derived from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), and thus from diffuse large B-cell lymphoma (DLBCL), occurs with splenomegaly, B symptoms, hypersplenism, and variable cytopenia [1]. Morphologically, it is composed of pale, variable sized micronodules localized predominantly in the white pulp. Containing small-sized T-cells and histiocytes in the background, the micronodules encompass a limited number of large neoplastic B-cells, mainly centroblasts or Hodgkin-Reed-Sternberg-like cells. The histopathological features are probably analogous with those displayed by the spleen involved by THRLBCL (25-67%), reaching stages III-IV (64%) [2]. In addition to pan-B markers (CD20; CD79a), these cells express BCL-6, some level of CD30, EMA and BCL-2, but not CD23, CD10, or EBER [1, 3, 4].

Since some MTLBLs affect the bone marrow, and less frequently liver or lungs, this variant lymphoma as a rule is not considered as a primary B-cell splenic lymphoma [5, 6].

The differential diagnosis of this lymphoma subset comprises mainly Hodgkin's lymphoma, mainly nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) [7]; DLBCL-NOS, THRLBCL, peripheral T-cell lymphoma, follicular lymphoma, and inflammatory granulomas.

In the absence of extensive clinical studies, and, relying on its being a variant of diffuse large B-cell lymphoma, the limited number of patients reported so far have been empirically treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), with a mainly although not entirely, poor outcome [1].

In the present study, an attempt is made to uncover the origin of the rare MTLBL variant. If indeed an association exists between MTLBL and THRLBCL, what is the trigger for the alteration? A thesis is advanced by which MTLBL may evolve following treatment with corticosteroids, prior to the diagnostic/therapeutic splenectomy.

Materials and Methods

The review is based primarily on three articles on MTLBL published by our group between 2008 and 2011 [8-10], since the results and conclusions thereof had not been interpreted to our complete satisfaction. Differences noted between MTLBL and THRLBCL had not been investigated in an exhaustive manner [1]. The apparently improved course in patients with corticosteroid premedication may carry a therapeutic significance, separate from the role of prednisone in the R-CHOP protocol. The features of the Beer-Sheva (Israel) MTLBL cases are summarized in a table, together with a single case with pre-diagnosis treatment with corticosteroids and reported from the Emory University Hospital [3] and will be compared primarily with the cohort reported by Dogan et al [1]. Moreover, the consequences evoked by these studies have not been translated into practical clinical resolutions. We are determined, therefore, to attempt the completion of our inquiry on this rare variant of diffuse large B-cell lymphoma. The present investigation will be established on the relevance of a pre-splenectomy corticoid therapy, on the splenic mass, on its morphology and on the clinical outcomes when available.

Clinical features of patients with MTLBL will be compared with those of patients with DLBCL-NOS, THRLBCL and NLPHL, regarding the propensity for splenomegaly in all four lymphomas.

Results

Unfolding the story

In 2008, Kan et al, reported on a 63-year-old woman who complained of fatigue, fever, and weight loss [8]. Blood exams revealed anemia, hypo- γ -globulinemia and elevated LDH. Splenomegaly was noted, but no peripheral lymphadenopathy was identified on physical examination or by computed tomography (CT) scan. A bone marrow biopsy showed paratrabecular infiltrates, including of large B cells. On splenectomy, the spleen weighed 540 g. Grossly, the white pulp was expanded, and the red pulp was preserved. Upon histology, the white pulp was invaded by micronodular infiltrates (Fig. 1A). Scattered CD20+ large tumor B cells, were found in a background of T-cells, histiocytes and eosinophils. A diagnosis of MTLBL was established. The patient was given 6 courses of R-CHOP. Complete remission was obtained and lasted 12 months, so far as the follow-up obtained. At the time of that report [8], Kan et al were not aware of the special significance of the patient's clinical and laboratory findings: hypersplenism, fever, and splenomegaly. They were not mindful of the special context of the pre-splenectomy corticosteroid treatment, administered for symptomatic relief.

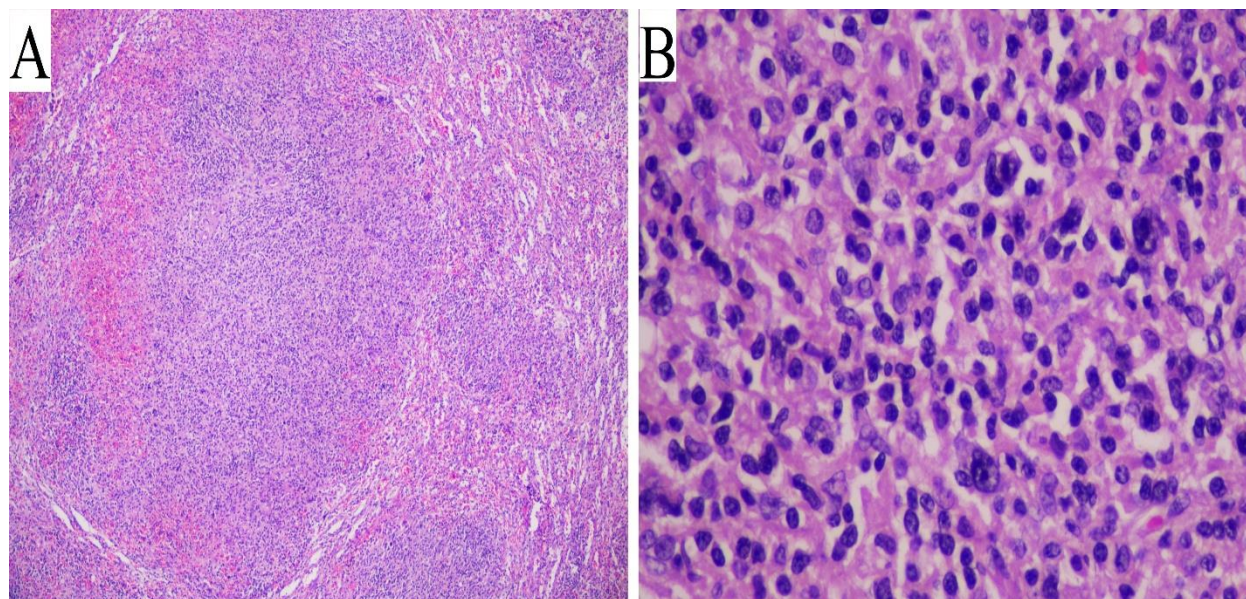


Figure 1.

The second episode

In an attempt, to explore the effects of corticosteroids on lymphoid cells and hematolymphoid neoplasms, Kan et al [9] identified 31 individuals who had been administered steroids prior to a diagnostic intervention. In addition to their inclusion in hematological chemotherapeutic protocols, glucocorticoids are prescribed for several inflammatory and autoimmune conditions.

While the above study was in progress, three additional patients from our medical center were identified who were suffering from MTLBL and had received steroid treatment prior to splenectomy. One of them was S.M., who had been described previously [8], but without being identified at that time as receiving corticosteroids. Thus, despite a compelling clinical context, the steroid pretreatment prescribed was overlooked, until revision [9, 10]. It is appreciated that this suggests that a similar negligence might recur, given the background conditions. A further MTLBL patient with prior corticoid therapy was described by Li et al as noted previously [3]. In this case, the spleen weighed 780 g.

Dogan et al [1] did not report on corticosteroid premedication among their 17 cases of MTLBL. This contrasts highly with the three cases described from Israel [8-10]. Splenomegaly in the Beer-Sheva group varied from 540 to 850 g, while in Dogan's cohort the range was 800 to 2500

g. It is postulated that, in the Israeli group, the reduction in the splenic mass may be attributed to steroid induced shrinkage of the splenic parenchyma [9]. Our hypothesis on a probable role of the corticosteroids, when administered before splenectomy, underlines their effect on the splenic size, its morphologic variance, as well as regarding the MTLBL disease outcome.

Regarding the histopathological diagnosis, apoptosis of the hematolymphoid cells, due to the steroid therapy, may have caused a reduction in the number of large B-cells. A similar effect on the background T-cells and histiocytes, might account for an increased difficulty in assuring a diagnosis [9, 10].

Glucocorticoid treatment may have affected the patients by additional means. Patient 2 shows micronodules that are sclerotic in part. This patient from the Emory University Hospital, was alive with lymphoma three months after surgery [3]. In cases 1 and 2 some epithelioid granulomas are found in the white pulp [3]. The three Israeli cases reached complete remission, lasting 12 to 36 months from diagnosis [8-10]. These findings contrast with Dogan's et al series, in which 7 of the 12 patients with follow-up, had died of the tumor within 2 years [1].

The most recent case of MTLBL, diagnosed at our medical center, features a 65-year-old-woman (L.Y.) living in a *kibbutz* (collective community) and employed at a faucet manufacturing plant. She had presented with recent weight loss, night sweats, and pancytopenia. Following an unremarkable bone marrow biopsy, a tru-cut splenic biopsy did not contribute any further to the diagnosis. Splenectomy revealed a spleen of 470 g with a nodular surface. The cut section displayed fine nodularity, entailing mainly the white pulp.

Immunophenotyping confirmed the picture displayed in our three prior cases: of note numerous small T-cells were found, without pan-T-cell restriction and with polyclonal TCRg and TCRb; and an excess of non-epithelioid histiocytes (Figure 1). A limited population of large B-cells displayed the immunophenotype: CD79a+; CD20-; BCL2+; BCL6+ and CD30+ (Figure 2). We are not aware of the cause of the CD20-negative expression in this patient's spleen, although we are positive that the large lymphoid cells are indeed large B cells. Moreover, a PCR analysis demonstrated a monoclonal immunoglobulin heavy chain (IgH) rearrangement.

A list of medications administered to this patient disclosed a prednisone treatment of 100 mg/day for 4 days. This "pulse" therapy was administered eight months prior to splenectomy. The

prescription was intended for a patient highly suspected for an aggressive lymphoma. Four months after diagnosis the patient is still undergoing R-CHOP therapy.

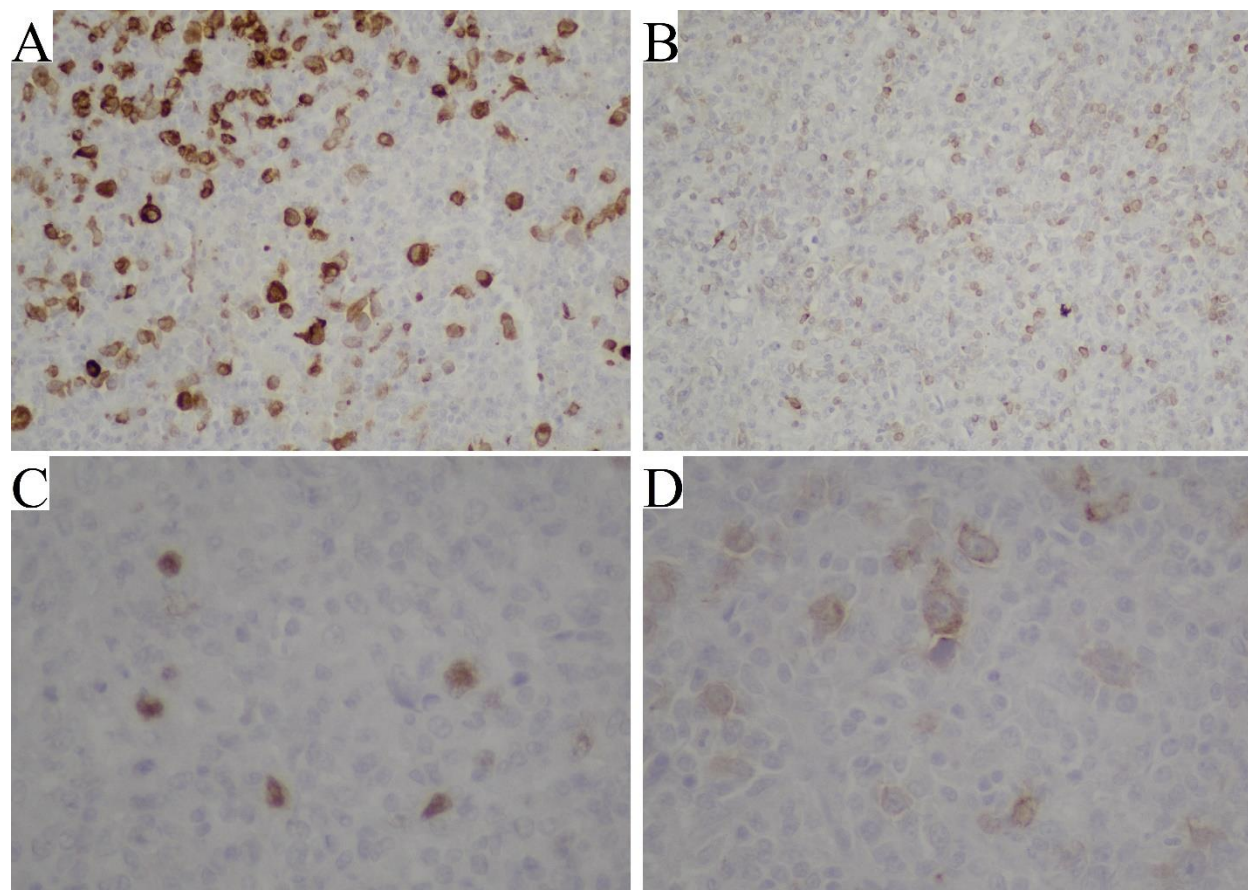


Figure 2.

The putative role of steroids prescribed prior to the diagnosis of lymphoma.

Various cells are affected differently by corticosteroids, by modification of the cellular metabolism or of gene expression. Lymphocytes are among the most affected [11]; these include thymocytes [12], T-lymphocytes [13], B-lymphocytes [14], monocytes and macrophages [15]. These cells are apparently reduced in number and/or in size.

Corticosteroids have also an immunosuppressive effect, which is noted in association with lymphomas. Primary central nervous system diffuse large B-cell lymphomas (DLBCL) seems to

be particularly prone to steroid treatment; post-treatment, high rates of non-diagnostic biopsies have been reported, and in several of the diagnostic biopsies there was extensive apoptosis with only few scattered large neoplastic cells identified on the background of abundant histiocytes [16]. Nevertheless, a mechanism is yet to be uncovered, suggesting a direct influence of steroids on lymphomas. Of note, corticoids have shown a capacity to initiate, as a single agent, the tumor lysis syndrome in aggressive lymphomas [17, 18].

Clinical features of the Israeli patients (Table 1)

The major role imputed to the corticoid-induced apoptosis in hematolymphoid conditions has been discussed [9]. Of the 31 pretreated patients mentioned by Kan et al [9], 8 were given corticosteroids for asthma; 2, for COPD; 5, for autoimmune hemolytic anemia; 3, for neurological symptoms; 3 for dermatoses; 2, for lung infiltrates, and another 10 for miscellaneous conditions. The corticosteroid dosage ranged from 2 mg/d for 10 years, to 100 mg/d for 4 days. Of note, two patients were treated with budesonide inhalation; two received dexamethasone for 1-2 days by injection.

Table 1. Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma – Israeli patients.

Patient	CR	BE	SM	LY	Emory
Age	70	59	61	65	73
Gender	F	M	F	F	F
Symptoms	Weight loss	B symptoms	B sym, pruritus	B sym, cytopenia	Anemia
Signs	Splenomegaly	Splenomegaly	Splenomegaly	Splenomegaly	Splenomegaly
Laboratory	Hemolytic anem	Anemia	Anem, hypogam	Pancytopenia	Anemia
Premedication	Prednisone	Prednisone	Prednisone	Prednisone	Prednisone
Dosage	60 mg/d	60 mg/d	40 mg/d	100 mg/d x4	unknown
Duration	6 m	Several m	3 m	4 d	3 m
Indication	Hemol anemia	F U O	Dermatitis	Susp. Lymphoma	Susp. sarcoid

Med. History	Asthma	OB. DM, Smoke	OB. DM. HB	DM	Granulomatous inflammation
Preliminary Dg	NHL	NHL	NHL	NHL	Sarcoidosis
Therapy	R-CHOP X 6	R-CHOP X 6	R-CHOP X6	R-CHOP X 6	Not mentioned
Clinical Outcomes	CR	MZBCL eye	CR	Ongoing primary treatment	AWD

Abbreviations:

FUO, fever of unknown origin

OB, obesity

DM, diabetes mellitus

NHL, non-Hodgkin lymphoma

CR, complete response

MZBCL, marginal zone B-cell lymphoma

The question of corticosteroid over-prescription was brought up to a highly experienced hematologist and co-author (IL). He agreed as to the tendency of internists and hematologists, at least in our area, to widely distribute corticosteroids to their patients, given a minimal indication. The low threshold for prescribing corticosteroids may cause an under-reporting of their use in medical communications, namely in pathology requisition forms, as seen for other widely used medications whose implication in histopathologic interpretation is minimal (e.g., acetaminophen and antihistamines). For the reasons presented in this manuscript, we are thoroughly opposed to the lack of transparency in steroid use on requisition forms, as well as caution against their overuse, given the possibility for ultimately creating diagnostic challenges.

An indication for corticosteroids premedication should probably be considered, in cases suspected of non-Hodgkin lymphoma, displaying B symptoms, splenomegaly and/or hypersplenism. This should be contemplated, especially if the preparatory phase for splenectomy is meant to be extended.

Comparison of MTLBL with DLBCL-NOS, THRLBCL and NLPHL (see Table 2)

MTLBL: stands out for the most marked splenomegaly, the most prominent B-symptoms, severe hypersplenism, together with variable cytopenia. Corticosteroid therapy, preceding splenectomy, may reduce the degree of the splenomegaly, the splenectomy complications, and it may significantly improve the outcome.

THRLBCL: affects predominantly males (1.7:1). It represents 10% of DLBCL-NOS. It shows a predilection for lymph nodes, but may affect the spleen as well, and, with rare exceptions will show a splenic morphology which is either multifocal or micronodular, as with MTLBL. The clinical picture at presentation includes high fever, splenomegaly, and advanced stages. Until recently, the prognosis was believed to be poor. However, this might not be the case anymore.

DLBCL-NOS: Half the cases emerge in stage I-II. The spleen is frequently enlarged, uni- to multicentric in structure, and the disease progresses rapidly. B-symptoms may occur. The 5-year survival is about 60%, pending the patient's age and stage.

NLPHL: No B-symptoms are present as a rule. The staging reaches III-IV in 10% of cases only, and splenomegaly occurs subsequently in this subset of patients. No splenectomy is carried out, as a rule, and the prognosis is overall favorable.

Table 2

Differential diagnoses of MTLBL and their clinical features

Entity	MTLBL	DLBCL, NOS	NLPHL	THRLBCL
Splenomegaly	Marked	Frequent	Only in late stages	Frequent
Lymph node regions	Splenic hilus	Variable	Superficial, mesenteric	Superficial, Deep
B-signs	Often	May be	None	Fever
Prognosis /5 years OS	Pending Splenomegaly, hypersplenism	60%	>80%	Pending histio-cytic population
Other clinical features	Variable cytopenia	50% stages I-II	10% stages III-IV	Lymphadenopathy

Histology (Large B-cells)	Centroblastic HRS-like cells	Centroblastic Immunoblastic Anaplastic	LP cells HRS-like cells	Centroblastic HRS-like cells
Immunophenotype of neoplastic cells	GC B-cell	GC or NGS	GC B-cell	GC B-cell

LP cells – lymphocyte predominant (popcorn) cells.

HRS-like cells – Hodgkin-Reed-Sternberg-like cells.

GC B-cell – Germinal Center B-cell.

NGS – Next Generation Sequencing.

Discussion

The taxonomy and histogenesis of splenic MTLBL remains unclear, in part because this subset is considered a variant of THRLBCL which itself is somewhat controversially considered a type of DLBCL-NOS according to the current (4th Revised, 2017) edition of the WHO Classification of Hematopoietic and Lymphoid Tumours, comprising by itself about 10% of all DLBCL's [2].

While earlier studies indicated that THRLBCL was a distinct clinicopathological entity with a more aggressive course than DLBCL [19-20], it was later revealed not to be the case and thought that THRLBCL was just a histologic variant on DLBCL [20]. Later studies still found greater similarity between this entity and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), both in terms of histology and (to various degrees) immunophenotype [20], as well as the epidemiology and clinical outcomes [21].

Although THRLBCL arises usually de novo, in some cases, in contrast, this lymphoma variant results from the progression of NLPHL. Of note, these two subsets are not easily segregated [2].

However, this issue has been dealt with extensively elsewhere and is not entirely relevant to this review.

A recent case report on a patient from Syria [22] even presents a “composite” lymphoma elaborated by THRLBL combined with NLPHL; we should be aware that in rare instances, authors might unnecessarily split a single clinical entity into two separate pathological diagnoses, based on subtle and perhaps insignificant variations. It is of note, that the spleen is involved much less frequently in NLPHL and that, only in advanced stages. Higher stages at presentation are rare [23, 24]. In one report, 4 of 35 patients with lymph-node-based NLPHL only exhibited splenomegaly at diagnosis [25]. Along those lines, just as nodal THRLBL was initially thought to be more aggressive than DLBCL, only later to be shown to have equal-to-or-better prognoses, thus, we keep an open mind, so that in the future, after the report of larger outcomes related to splenic MTLBL, the prognosis may be more favorable than it has originally seemed.

Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma, considered by many as associated with the mainly nodal THRLBCL, is a rare variant large B-cell lymphoma [26, 27]. However, THRLBCL mainly affects lymph nodes, with only limited involvement of bone marrow, liver, lungs, and spleen. In MTLBL, splenomegaly is the predominant trait, accompanied by hypersplenism and B symptoms. When present, involved lymph nodes are restricted to the splenic hilar region. Most of the cases described present with splenomegaly of variable degree, hypersplenism and cytopenia, and fewer numbers have fever. In only a few patients the disease involves sites beyond the spleen and splenic hilar lymph nodes. Why do the changes concern the spleen, liver, bone marrow, lungs and selectively the splenic hilar lymph nodes, and are not found, as a rule, in peripheral or deep lymph nodes, which are involved preferentially in the THRLBCL?

The presenting symptoms, mainly hypersplenism, when associated with a relatively long period of observation and of preparation for the splenectomy, have evoked the necessity for steroid premedication. In THRLBCL, the response to chemotherapy is poor. Although prednisone is often part of the treatment protocol, a separate response to corticosteroids has not been assessed.

Regarding two Israeli MTLBL patients, the reviewers overlooked completely or temporarily, the corticosteroid pretreatment. It might be a stretch to assume a similar oversight in 17 unrelated patients [1]. On the other hand, we cannot establish unequivocally that Dogan's patients did *not* receive pre-splenectomy corticosteroids. While the differences in the severity of splenomegaly must still be displayed in Dogan's cohort when compared to the Israeli group, the similarities in morphology support that probably both groups of patients did receive corticoid pretreatment. Future discussions on the morphology of lymphoproliferative neoplasms in general, and certainly MTLBL and THRLBCL specifically, should explicitly mention the use or lack thereof for pre-excision corticosteroids.[1]

Conclusion

The apparent, complete absence of a corticoid premedication in all the cases of MTLBL from most cases recorded, is contrasted with the four cases diagnosed in Beer-Sheva, Israel, and with a single case from Emory university Hospital all of which were given steroid pretreatment. Glucocorticoids were administered to three of the four Israeli patients in relation to the ongoing disease: hemolytic anemia, fever of unknown origin, and weight loss. In the fourth, the pretreatment was directed at dermatitis. The case reported by Li et al was pretreated with corticoids following the suspicion of sarcoidosis [3].

Evidence is presented of a significant role for corticosteroid premedication prior to splenectomy in MTLBL regarding an apparent transformation from the classic THRLBCL morphology from which the splenic form of the disease is derived. Indications for its prescription comprises on the one hand splenomegaly, B symptoms, hypersplenism, with or without cytopenia. On the other hand, intercurrent conditions, like asthma, COPD, and so on, might serve as a pretext, in case the patient is highly symptomatic, but does not exhibit specific symptoms and signs of the lymphoma. A limitation in our narrative regards the degree of confidence attributed to corticosteroid therapy in MTLBL. This medication, pertinent if the four Israeli patients could be classified as stages III or IV of the non-Hodgkin's lymphoma, right prior to the prednisone prescription. However, such a query remains insoluble, as one may never know what the stage might be immediately before splenectomy. The issue is equally pertinent for staging in the remaining MTLBL cases [28, 29]. Our thesis, surmising that a greater proportion of MTLBL

patients had undergone pre-diagnostic corticosteroid treatment than formerly realized, may be admissible.

We have refrained from addressing the complex issues concerning the interrelations between THRLBCL and NLPHL, because of the lack of relevance to the main theme of this review [30]!

Figure 1A. Section of the spleen of L.Y. A micronodule is found in the white pulp, surrounded by generally preserved red pulp (H&E x40).

Figure 1B. A close-up view of the micronodule in Fig. 1A, displaying a lymphoid infiltrate, composed mainly of small lymphocytes, histiocytes and sparse large lymphoid cells (H&E x400).

Figure 2A-D. Immunophenotype of the large lymphoid cells within the splenic micronodules. A pan-B-cell marker (CD79a) is positive (A). BCL-2 is expressed in the large lymphoid cells (B). BCL-6 is expressed in scattered large lymphoid cells (C). CD30 is positive in the large cells (D).

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Author Contributions

BS: Resources, Visualization, Writing – Review & Editing; *KN*: Investigation, Resources, Visualization, Writing – Review & Editing; *DB*: Investigation, Methodology, Project Administration, Supervision, Writing – Original Draft; *IL*: Resources, Writing – Review & Editing

Institutional Review Board Statement

The manuscript was not presented to an IRB for approval.

Informed Consent Statement

The patient with the most recent case of MTLBL, being presented in this paper for the first time, has signed a consent form for a case study to be published.

Conflicts of Interest

The authors declare no conflict of interest.

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