

## ORIGINAL ARTICLE

# Granulomatous reactions cause symptoms or clinically imitate treatment resistance in small lymphocytic lymphoma/chronic lymphocytic leukaemia more frequently than in other non-Hodgkin lymphomas

A Brunner, J Kantner, A Tzankov

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**Aims:** The electronic database of the institute of pathology, Medical University of Innsbruck, was reviewed and patient histories studied to analyse systematically the coincidence of granulomatous reactions and lymphomas in a large patient collective, and to find distinct clinicopathological correlations. Five cases of small lymphocytic lymphoma/chronic lymphocytic leukaemia (CLL) associated with granulomatous reactions in lymph nodes and bone marrow were identified, all clinically associated with signs of progressive disease.

**Methods:** Cases were acquired by reviewing an electronic database comprising approximately 715 000 patients diagnosed between 1993 and 2003. Histochemical, immunohistochemical, and molecular techniques were used to verify diagnosis and associated infectious diseases. Clinical data were obtained from reviewing the charts.

**Results:** Of 2044 bone marrow and 411 lymph node non-Hodgkin lymphoma biopsy samples, CLL was most frequently associated with bone marrow (two cases) and lymph node granulomas (three cases). These granulomas were mostly composed of epithelioid cells, with or without giant cells, and in all but one case did not show necrosis. All patients with CLL had clinical symptoms primarily caused by the granulomatous disease: two suffered from acid fast bacilli infections (*Mycobacterium tuberculosis* and mycobacteria other than tuberculosis) and three presented with clinical manifestations of sarcoidosis (the reason a diagnostic biopsy was performed).

**Conclusions:** Granulomatous reactions in patients with CLL might obscure diagnosis and imitate disease progression and Richter's transformation. Careful histological examination, exclusion of infectious agents, and a detailed clinical history are essential for correct diagnosis.

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In lymph nodes from European patients, so called sarcoid-like lesions represent one of the most common granulomatous reactions, seen most frequently in the draining lymph nodes of solid tumours. In haematological disorders, sarcoid-like lesions are often seen in Hodgkin lymphomas (HL), and have also been found in approximately 4% of non-Hodgkin lymphomas (NHL)<sup>1–14</sup> (table 1). Furthermore, patients with lymphoma are at an increased risk of developing disease and treatment related infectious complications, especially by opportunistic microorganisms, such as mycobacteria other than tuberculosis, pneumocystis, and fungi, all of which may also lead to granuloma formation.<sup>13–15</sup> Interestingly, the development of extensive sarcoid-like lesions and sarcoidosis in patients with lymphoma and, vice versa, a higher risk of developing lymphomas in patients with sarcoidosis (the "sarcoidosis-lymphoma syndrome"), have also been documented.<sup>1 16–20</sup> Granulomas are rarely found in trephine bone marrow biopsies.<sup>13</sup> They are found in approximately 30% of cases associated with infectious diseases, with *Mycobacterium tuberculosis* and *Mycobacterium avium intracellulare* being responsible for nearly half of these cases.<sup>13</sup> Apart from infections, bone marrow sarcoid-like lesions can be associated with haematological malignancies and, in decreasing frequency, with non-hematological malignancies, sarcoidosis, and drugs.<sup>13–15 21 22</sup> Table 1 shows an overview of the reported coincidence of lymphomas and granulomas in bone marrow and lymph nodes. To the best of our knowledge, in the past 52 years only 69 NHL cases accompanied by

sarcoid-like lesions or accumulation of histiocytes in either bone marrow or in the lymph nodes have been reported.<sup>1–14</sup> These cases have been classified according to different nomenclature systems, making a direct comparison impossible. In the above mentioned studies, small lymphocytic lymphomas did not appear to be over proportionally associated with sarcoid-like lesions, and the causes of granuloma formation have not been studied extensively.

"Patients with lymphoma are at an increased risk of developing disease and treatment related infectious complications, which may also lead to granuloma formation"

Therefore, to analyse systematically the coincidence of granulomatous reactions and NHL, on a large patient collective, and to discover distinct clinicopathological correlations, we reviewed the electronic database at the institute of pathology at the Medical University of Innsbruck, Austria, looking for patients with lymphomas and granulomatous reactions in their bone marrow and lymph nodes, and studied case histories of patients suffering from both.

**Abbreviations:** CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia; HL, Hodgkin lymphoma; IFN, interferon; NHL, non-Hodgkin lymphoma; PCR, polymerase chain reaction

**Table 1** Reported bone marrow and lymph node granulomatous reactions in lymphomas

First author	Location	Histology	Bone marrow and lymph node granulomatous reactions in lymphomas				Total number of cases examined
			HL	%	NHL (according to different classification systems)	%	
Pease <sup>5,6</sup> Kim <sup>7</sup>	BM LNs	SG SG	8	3.6%	7 NHL, not specified; 2 multiple myelomas 1 nodular mixed histiocytic-lymphocytic lymphoma; 2 histiocytic lymphomas	4% 3.5%	221 HL and NHL 84 untreated NHL CLL, and Mb; Waldenström excluded 608 HL 107 HL 9 cases observed
Sacks <sup>3</sup> O'Carroll <sup>8</sup> Yu <sup>9</sup>	BM, LNs BM BM	SG SG SG	17 6	2.8% 5.6%	1 nodular poorly differentiated lymphoma; 2 diffuse poorly differentiated lymphomas; 4 diffuse histiocytic lymphomas; 1 diffuse mixed histiocytic-lymphocytic lymphoma; 1 unclassified splenic lymphoma 3 poorly differentiated lymphocytic lymphomas; 3 histiocytic lymphomas; 3 MMs; 1 acute lymphoplastic leukaemia		
Choe <sup>10</sup>	BM	SG			8 NHL, not specified; 1 acute lymphoblastic leukaemia; 1 CLL 1 MM	2.6%	372 NHL
Bhargava <sup>13</sup>	BM	SG	7	0.1% of all biopsies	11 "Lennert" lymphomas of B and T cell origin 5 Burkitt lymphomas; 2 follicular lymphomas	0.16% of all biopsies	6988 bone marrow biopsies; 72 specimens with granulomas 355 NHL
Spier <sup>11</sup>	LNs	SG			1 immunocytoma 1 diffuse large B cell lymphoma	3.1%	7 cases observed
Hollingsworth <sup>2</sup>	BM	Clusters of histiocytes			3 CLL 4 Burkitt lymphomas		Single case observed Single case observed 3 cases observed 67 Burkitt lymphomas
Dunphy <sup>4</sup> Kornacker <sup>1</sup> Blanco <sup>14</sup> Haralambieva <sup>12</sup>	LNs BM LNs LNs	SG SG NG SG				6%	

BM, bone marrow; CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia; HL, Hodgkin lymphoma; LN, lymph node; Mb, myeloblastoma; MM, multiple myeloma; NG, necrotising granulomas; NHL, non-Hodgkin lymphoma; SG, sarcoid granulomas.

## MATERIAL AND METHODS

### Cases

Cases were acquired by reviewing the electronic database of the institute of pathology at the Medical University of Innsbruck, Austria, comprising approximately 715 000 case files over the observation period from 1993 to 2003, looking for the coincidence of haematological neoplasms and granulomatous reactions in lymph nodes and in bone marrow biopsies. The search was performed by looking for the simultaneous occurrence of the letter combinations "LYMPHOM" or "LEUK" and "GRANULOM" or "EPITHEL" within the diagnosis paragraphs.

### Clinical data

The clinical data of the patients with granulomatous reactions in the setting of NHL were obtained by reviewing the charts (table 2).

### Histochemical and immunohistochemical stainings

Special stains for acid fast bacilli (Ziehl-Neelsen, Fite-Faraco) and fungi (periodic acid Schiff) were performed. Immunohistochemistry was performed in an automated

immunostainer (Nexes; Ventana, Tucson, Arizona, USA), applying the streptavidin-biotin-peroxidase technique with diaminobenzidine as chromogen. The primary antibodies comprised anti-CD3 (Dako, Glostrup, Denmark; 1/50 dilution), anti-CD4 (Novocastra, Newcastle upon Tyne, UK; 1/10 dilution), anti-CD5 (Novocastra; 1/50 dilution), anti-CD8 (Dako; 1/50 dilution), anti-CD20 (Dako; 1/700 dilution), anti-CD23 (Novocastra; 1/40 dilution), anti-CD68 (Dako; 1/100 dilution), anti-CD79 (Dako; 1/300 dilution), and KiM1P (Dako; 1/300 dilution). Heat pretreatment in a wet autoclave at 121°C with citrate buffer (pH 6.0) for five minutes was used for antigen retrieval, except for KiM1P and CD20, for which pretreatment with pronase for eight minutes at room temperature and heat pretreatment in a microwave oven (750 W) for 10 minutes were used, respectively.

### Molecular biology

To detect genetic material from *M tuberculosis* the total DNA from the formalin fixed, paraffin wax embedded tissue samples of the patients was extracted using a Genovision (Qiagen, Hilden, Germany) extraction kit. For polymerase chain reaction (PCR) we used primers synthesised by an

**Table 2** Patients' clinical data

Case	Sex	NHL	Clinical manifestations at diagnosis of granuloma	IFN $\alpha$	Age*	Age†	Follow up (months)	Outcome
1	M	CLL	Cough, suspicious pulmonary lesions with lymphadenopathy	No	72	72	120	Alive
2	F	CLL	Indolent axillar, cervical, and bihilar lymphadenopathy	No	74	74	18	Alive
3	F	CLL	Bihilar lymphadenopathy resistant to cytotoxic treatment	Yes	54	65	133	Alive
4	F	CLL	Rapidly growing generalised lymphadenopathy, fever	No	63	71	93	Dead
5	M	CLL	Rapidly growing mediastinal lymphadenopathy, fever	No	41	55	169	Alive

\*Age at diagnosis of NHL; †age at diagnosis of granulomas.

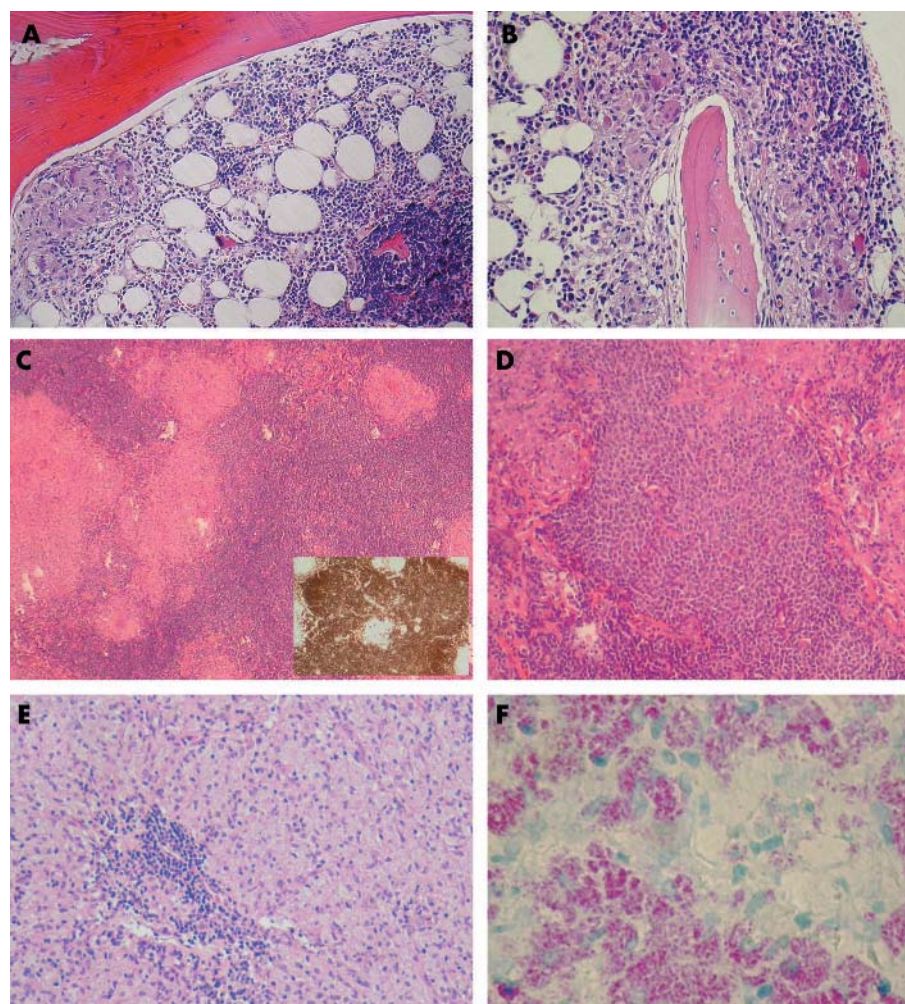
CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia; IFN, interferon; NHL, non-Hodgkin lymphoma; TBC, tuberculosis.

automated DNA synthesiser (GenXpress, Maria Woerth, Austria) against the *M tuberculosis* complex specific target IS6110 repetitive element, as described by Lachnik and co-authors,<sup>23</sup> and a commercially available ready to use Taq man buffer containing Taq polymerase, reaction buffer, and dNTPs (Applied Biosystems, Rotkreuz, Switzerland). PCR was performed for 50 cycles; the amplification products were visualised using a 121 bp specific fluorescent labelled probe that recognises the IS6110 repetitive element PCR copies in an ABI prism 7000 real time PCR cyler (Applied Biosystems).

**RESULTS**

Between 1993 and 2003 approximately 715 000 cases were evaluated at our institute, of which 10 472 were bone marrow biopsies; 2044 bone marrow biopsy specimens were infiltrated by NHL and only three by HL; 981 samples were diagnosed as chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL). In the same period, 411 primary nodal NHLs were diagnosed. Independent of the primary diagnosis, within the observation period, sarcoid-like lesions were diagnosed in 56 lymph nodes, 37 of which were associated with solid neoplasms, three with HL (two classic HL and one nodular paragranuloma), and one with synchronous CLL (patient 2). We identified two more patients with CLL from all of the patients diagnosed with NHL with synchronous (patient 1) or metachronous (patient 3) sarcoid-like lesions in their bone marrow biopsies. Two additional patients with

CLL from our database had lymph node granulomas in the setting of infection with *M tuberculosis* (patient 4) and mycobacteria other than tuberculosis (patient 5). All patients with HL and sarcoid-like lesions presented with B symptoms, but had no additional peculiarities in their clinical history. Unexpectedly, all patients with CLL and granulomatous reactions had a distinct clinical history (table 2). Three patients presented with manifestations that typically occur in sarcoidosis (bihilar lymphadenopathy, arthralgia, increased angiotensin converting enzyme concentrations; patients 1, 2, and 3). In addition, in patients 1 (fig 1A) and 2 the diagnostic biopsy was performed because of the progressive lymphadenopathy suspicious of sarcoidosis, and coincidental (synchronous) “dormant” CLL with sarcoid-like lesions was diagnosed histologically. The detection of concomitant CLL in the lymph node of patient 2 was difficult (fig 1C, D); lymphocytic infiltration beyond the lymph node capsule, the disappearance of hilar structures as a result of expansion, and the monotonous lymphocytic morphology were important morphological keys to consider ancillary immunohistochemical studies for diagnosing CLL. In patient 3, CLL was known and Richter’s syndrome was clinically suspected because the progressive bihilar lymphadenopathy was resistant to the fludarabine/interferon  $\alpha$  (IFN $\alpha$ ) treatment regimen (fig 1B). Therefore, a newly staging bone marrow biopsy was performed, which showed a sarcoid-like lesion and only minimal residual CLL. CLL was also known in patients 4 and 5. They developed rapidly progressive lymph node swellings



**Figure 1** (A) Peritabecular sarcoid-like lesion and a small nodular chronic lymphocytic leukaemia infiltration (original magnification,  $\times 200$ ). (B) Peritabecular sarcoid-like lesion intermingled with scant chronic lymphocytic leukaemia cells (original magnification,  $\times 200$ ). (C) Coincidental small lymphocytic lymphoma and sarcoid-like lesions in a lymph node (original magnification,  $\times 40$ ); insert: lymphoma population positively stained with anti-CD79a antibodies; note the negative sarcoid-like lesions (original magnification,  $\times 40$ ). (D) Coincidental small lymphocytic lymphoma and sarcoid-like lesions in a lymph node; note the epithelioid cells and typical lymphoma cells (original magnification,  $\times 200$ ). (E) Diffuse foamy cell infiltration in a case of *Mycobacterium avium intracellulare* infection in a patient with small lymphocytic lymphoma; note the isolated lymphocytic rests (original magnification,  $\times 200$ ). (F) Large numbers of acid fast bacilli in a case of *M avium intracellulare* infection stained by the Ziehl-Neelsen method (original magnification,  $\times 400$ ).

with fever and increased lactate dehydrogenase, clinically suspicious of Richter's syndrome; patient 5 had recently undergone cyclophosphamide/ondovine/prednisone chemotherapy. The patients were diagnosed as infected with *M tuberculosis* and mycobacteria other than tuberculosis (*M avium intracellulare*), respectively (fig 1E, F), involving the mediastinal lymph nodes and, in patient 5, the small intestine. Both patients were given specific treatment, but patient 4 unfortunately died of septicaemia. Table 3 summarises the results of the special stains, location, and histology of the granulomas associated with CLL.

## DISCUSSION

Although the presence of granulomatous reactions in patients with NHL is known, they have been rarely observed in CLL.<sup>13 14 24</sup> In our study group, all five patients with CLL became symptomatic as a result of a granulomatous process within the setting of their previously or newly (patients 1 and 2) diagnosed NHL. Three patients had sarcoid-like lesions, and sarcoidosis, and two suffered from mycobacterial infections.

Sarcoid-like lesions represent non-specific histological patterns that may be associated with viral infections, tuberculosis, sarcoidosis, or lymphoproliferative disorders, so that in addition to a careful histological examination, special stains and PCR analyses should be performed to exclude the presence of an infectious agent.<sup>14 15</sup> Although a distinction is made between sarcoid-like lesions and sarcoidosis, some evidence points to the possibility that sarcoidosis represents a generalised equivalent of sarcoid-like lesions that may be caused by phospholipids from necrotic material or chronic antigen stimulation.<sup>20 25 26</sup> In sarcoid-like lesions, putative (for example, tumour derived) antigens are thought to cause a hypersensitivity reaction mediated by T cells that stimulate monocytes to form an epithelioid granuloma.<sup>2</sup> Several authors noted the presence of both sarcoidosis and NHL in the same patient.<sup>1 17 20 24 27</sup> Chemotherapy may be one reason for the development of sarcoid-like lesions. So far, only IFN $\alpha$  is known to induce sarcoidosis/sarcoid-like lesions.<sup>18 27</sup> Continuous IFN $\alpha$  administration in viral infection can activate T cells and macrophages.<sup>18</sup> An accumulation of CD4<sup>+</sup> T cells has been seen in IFN $\alpha$  associated skin eruptions.<sup>19</sup> Indeed, in our study, one female patient with CLL developed fludarabine/IFN $\alpha$  resistant bihilar lymphadenopathy, with an increased angiotensin converting enzyme concentration (62 U/litre) and raised local CD4/CD8 ratio in the bone marrow sarcoid-like lesions, and therefore was diagnosed as suffering from sarcoidosis. Interestingly, all these symptoms, including the bihilar lymphadenopathy, resolved after withdrawing IFN $\alpha$  treatment. Kornacker *et al* noted sarcoidosis in two patients with NHL without IFN

## Take home messages

- Granulomatous reactions might obscure diagnosis in patients with undiagnosed small lymphocytic lymphoma/chronic lymphocytic leukaemia (CLL) or imitate disease progression and Richter's transformation in those with known CLL
- Careful histological examination including special stains, exclusion of infectious agents by molecular techniques, and a detailed clinical history, including treatment with interferon  $\alpha$ , are essential for a correct diagnosis

treatment and made the intriguing suggestions of (1) a probable spread of an infectious agent during immunosuppression leading to granuloma formation, or (2) chemotherapy induced elimination of immunosuppressive cells that inhibit immune activation resulting in sarcoid-like lesion formation.<sup>1</sup>

To date, sarcoid-like lesions have only rarely been seen in the lymph nodes and bone marrow of patients with CLL. Choe *et al* investigated 372 cases of bone marrow granulomas and found no cases of CLL, whereas Bhargava and Farhi reported one case of CLL in 21 patients with haematological diseases associated with sarcoid-like lesions.<sup>10 13</sup> Marruchella *et al* reported the case of a 59 year old woman with CLL treated with chlorambucil and fludarabine, who subsequently developed sarcoidosis with diffuse lung involvement and bihilar lymphadenopathy.<sup>24</sup> In our study, most of the patients with haematological neoplasms and concomitant granulomatous (especially sarcoid-like) lesions had CLL, perhaps in part because of the frequent occurrence and long clinical history of CLL, similar to that seen in testicular germ cell tumours.<sup>24</sup> However, studies on T cell function in CLL have revealed a wide range of abnormalities, including absolute CD8<sup>+</sup> lymphocytosis and abnormalities in ligand expression. The elimination of specific CD8<sup>+</sup> immunosuppressive cells and CD4<sup>+</sup> T helper type 1 and 2 cell subsets through chemotherapy might also contribute to sarcoid-like lesion formation.<sup>1 28</sup> Furthermore, treatment associated T cell dysfunction and subset disturbances in CLL, such as specific loss of CD4<sup>+</sup> helper cells—induced by alkylating agents, purine analogues, especially fludarabine, and steroids<sup>29 30</sup>—lead to disturbed immune surveillance for infections, especially those caused by mycobacteria, *Listeria monocytogenes*, pneumocystis, *Candida* spp, *Aspergillus* spp, cytomegalovirus, varicella zoster virus, and herpes simplex virus, all of which may trigger granuloma formation.<sup>13–15 28</sup> The treatment

**Table 3** Histological, histochemical, and immunohistochemical findings

Case	Granuloma location	Histology	CD4/CD8*	Ziehl-Neelsen	PAS	Fite-Faraco	TBC-PCR
1	BM	Microgranuloma, no giant cells; CLL	1/1	Negative	Negative	Negative	Negative
2	LN	Circumscribed granulomas, epithelioid and Langhans giant cells; CLL	5/1	Negative	Negative	Negative	Negative
3	BM	Circumscribed granulomas, epithelioid cells, no giant cells; CLL	10/1	Negative	Negative	Negative	Negative
4	LN	Necrotising granulomas, epithelioid and Langhans giant cells; CLL	2/1	Positive	Negative	Negative	Positive
5	LN	Large granulomas, foamy macrophages; CLL	No T cells	Positive	Positive	Positive	Negative

\*Within the granulomas.

BM, bone marrow; CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia; LN, lymph node; PAS, periodic acid schiff; PCR, polymerase chain reaction; TBC, tuberculosis.

associated T cell dysfunctions in CLL result mainly from the fact that the therapeutic agents used inhibit not only lymphocyte RNA and DNA synthesis and repair, but also cytokine induced STAT1 activation, and interfere with the interleukin 2 cascade, which is essential for cell mediated immunity function.<sup>30 31</sup> Indeed, we found severe mycobacterial infections in two patients with CLL, one of whom unfortunately died of septicaemia. Clinically, both patients presented with a rapidly progressive generalised lymphadenopathy and lactate dehydrogenase increase, but low leucocyte counts, so that Richter's transformation was clinically suspected, although the first histological examination detected mycobacteriosis.

In summary, symptoms caused by granulomatous reactions can occasionally lead to the detection of an otherwise dormant CLL or, in cases with known CLL, clinically mimic disease progression or treatment resistance. Treatment with IFN $\alpha$ , but also infections, especially mycobacterioses, and CLL related or treatment induced changes in lymphocyte communication may cause granulomatous reactions. Careful histological examination applying special staining procedures, combined with modern methods for molecular detection of infectious agents, considering also details of the clinical history, should lead to the correct diagnosis.

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