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Pathology in Focus

The blastic variant of mantle cell lymphoma arising in Waldeyer's tonsillar ring

NADINE S. IVES AGUILERA, M.D., M. UUSAFR*, BRUCE M. WENIG, M.D.†, SUSAN L. ABBONDANZO, M.D.*

Abstract
We present three cases of blastic mantle cell lymphoma with an unusual initial manifestation in Waldeyer's ring with methods for differentiating it from other blastic neoplasms of the head and neck. All cases presented with a feeling of fullness in the area of the mass. Morphologically, the tumours were blastic with a high mitotic rate (three to nine per high power field). All were B-cell phenotype with coexpression of CD43. In all cases cyclin D1 and bcl-2 were positive and CD23 negative. Blastic mantle cell lymphoma occurring in Waldeyer's tonsillar ring may be mistaken for other high grade haematopoietic neoplasms. Immunohistochemistry and awareness of this type of lymphoma are helpful in differentiating it from other neoplasms.

Key words: Lymphoma, B cell mantle; Tonsil neoplasms; Nasopharyngeal neoplasms; Tongue neoplasms

Introduction

Mantle cell lymphoma (MCL) is a non-Hodgkin's lymphoma which has a marked male predominance that typically is nodal-based but can involve extranodal sites (Lardelli *et al.*, 1990; Fraga *et al.*, 1995; Pittaluga *et al.*, 1995; Weisenberger and Armitage, 1996). Among the more common extranodal sites of involvement are the mucosa of the gastrointestinal tract and upper aerodigestive tract, stomach, large intestine and tonsils. MCL shares clinical properties of both low- and higher-grade malignant lymphomas. Similar to low-grade lymphomas, MCL often involves the bone marrow at the time of diagnosis (Fraga *et al.*, 1995; Pittaluga *et al.*, 1995; Weisenberger and Armitage, 1996) and may involve the peripheral blood (Pombo De Oliveira *et al.*, 1989; Vadlamudi *et al.*, 1996). Further, MCL tend to be resistant to treatment with difficulty in eradicating the tumour following therapy. However, classic MCL properties which are unusual for low-grade lymphoma and more like that of intermediate to high-grade lymphomas, include moderately aggressive behaviour with a relatively short survival (mean 35 months) (Lardelli *et al.*, 1990; Fraga *et al.*, 1995; Pittaluga *et al.*, 1995; Weisenberger and Armitage, 1996) and the potential for blastic transformation rather than a large cell transformation. Blastic transformation of MCL (BMCL) is a rare event at presentation (Lardelli *et al.*, 1990; Pittaluga *et al.*, 1995), but over time, with subsequent biopsies of MCL, it may become more common (Norton *et al.*, 1995). BMCL is characterized by a diffuse growth pattern, nuclei with dispersed chromatin, indistinct nucleoli, and increased mitotic rate (Lardelli *et al.*, 1990; Fraga *et al.*, 1995; Norton *et al.*, 1995; Pittaluga *et al.*, 1995; Weisenberger and Armitage, 1996). We report three cases of BMCL initially occurring in Waldeyer's ring, detailing their clinicopathological findings and immunophenotype.

Case reports

All three patients were male, aged 50, 70 and 74 years. The location of the tumours were left tonsil (*Case 1*), nasopharynx (*Case 2*), and base of tongue (*Case 3*). The clinical presentation for all patients was a feeling of fullness in the area of the mass. The duration of symptoms was difficult to determine from the patient history, and clinical and laboratory findings were limited. None of the patients had any prior history of a lymphoproliferative disorder, neoplasm or previous radiation to the head and neck. No lymphadenopathy was present in any of the patients.

Following the histological diagnosis (see below), each patient was extensively evaluated. *Case 1*, a 70-year-old man with tonsillar lymphoma, showed bone marrow involvement one month after the initial biopsy. Following the bone marrow biopsy, the patient had radiation to the neck and supraclavicular area, and to the nasopharynx and tonsil. The patient had an abdominal reoccurrence at 19 months and chemotherapy was given. The patient is alive at 32 months in clinical remission.

Case 2, a 50-year-old man with nasopharyngeal lymphoma, showed no systemic disease at diagnosis but was lost to follow-up without treatment.

From the Departments of Hematopathology*, and Otolaryngologic and Endocrine Pathology†, Armed Forces Institute of Pathology, Washington D.C.
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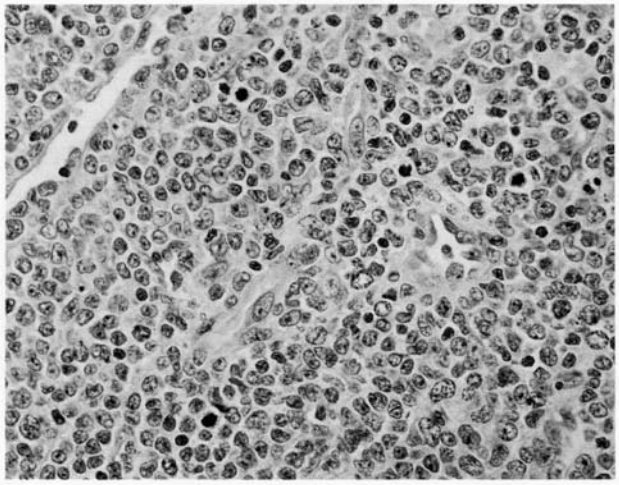

FIG. 1

A section from the tonsil in *Case 1* shows the typical cytological features of the blastic variant of MCL (BMCL): slightly cleaved nuclei with blastic nuclear chromatin and a high mitotic rate (H & E; × 300).

Case 3, a 74-year-old man with lymphoma of the base of the tongue, had gastric and bone marrow involvement one month after diagnosis. The patient died of disease near the time of bone marrow and gastric biopsy. An autopsy was performed which showed that the patient died with extensive gastrointestinal lymphoma.

Pathology

The histology of *Cases 1* (Figure 1) and *2* were similar to each other and showed characteristic features of BMCL. *Case 3* also had dispersed chromatin with indistinct nucleoli as the other cases, but showed more variation in cell size and irregularity (Figures 2a and 2b). The mitotic rate was brisk in all cases with *Case 1* having 9.5 mitotic figures per high power fields (hpf)(95/10 hpf), the other two cases had similar rates to each other with approximately 3.8 (38/10 hpf) and 3.2 (32/10 hpf) mitoses/hpf respectively. Interspersed histiocytes created a 'starry sky' appearance in *Case 2* (nasopharynx). The other two cases showed focal epithelioid histiocytes but not a 'starry sky'

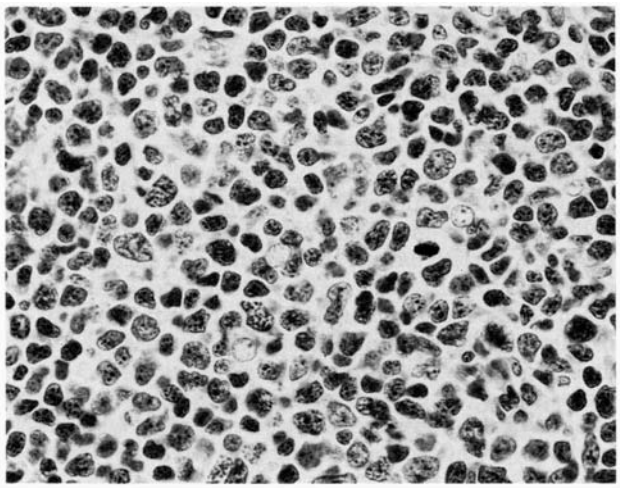

FIG. 2b

Cytologically the cells are small to medium-sized cells with slightly cleaved nuclei and finely dispersed chromatin. The cells in this case vary in size and shape and may correspond to the 'anaplastic variant' described by Ott *et al.*, (H & E; × 400).

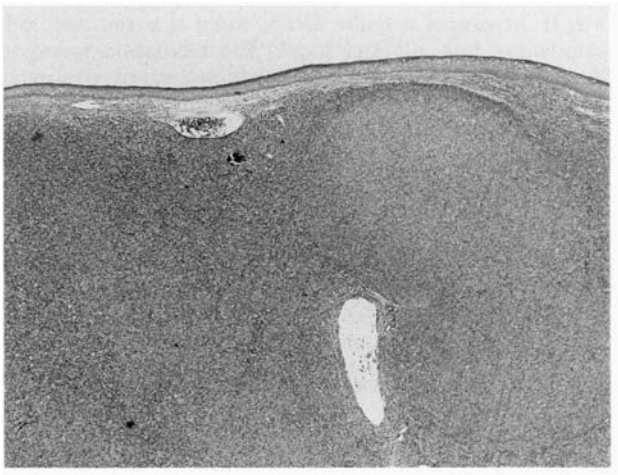

FIG. 2a

A diffuse infiltrate at the base of the tongue (*Case 3*) showing a monotonous appearance of small-medium sized blastic cells (H & E; × 10).

appearance. Focal areas of classic MCL were seen in all cases, which showed small cell size with slightly cleaved nuclei and lack of transformed cells or immunoblasts. These areas were vaguely nodular.

All cases had a B-cell immunophenotype (CD45RB and CD20 immunoreactive) with scattered reactive small CD3 or CD45RO positive T-cells. CD43 and bcl-2 were co-expressed in the malignant B-cells in all cases. Cyclin D1 was positive in all of our cases (Figure 2c) with *Case 1* showing weak immunoreactivity. CD5 was weakly immunoreactive in *Case 2*. LMP-1 for Epstein-Barr virus, TdT and CD23 were negative in all cases.

Discussion

Blastic MCL is an uncommon initial diagnosis and may represent a terminal progression of MCL. Blastic differentiation is characterized by the presence of cells with dispersed chromatin, indistinct nucleoli, and a higher mitotic rate than seen in the classic form of MCL (Lardelli *et al.*, 1990; Fraga *et al.*, 1995; Norton *et al.*, 1995; Pittaluga *et al.*, 1995; Weisenberger and Armitage, 1996). The percentage of cases of MCL having blastic transformation has been reported to range from five per cent (three) to

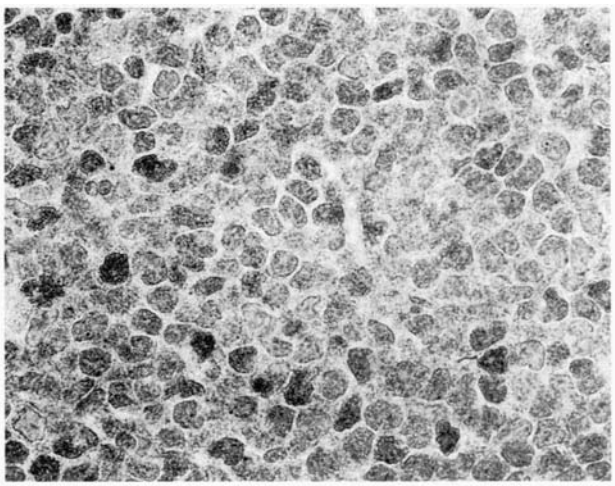

FIG. 2c

Nuclear immunoreactivity for cyclin D1 in the neoplastic cells in *Case 3* (cyclin D1; × 480).

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greater than 25 per cent (two) on the initial biopsy; with a greater percentage of MCL showing blastic morphology on rebiopsy (Norton *et al.*, 1995). The survival period for patients with BMCL is shorter than that for patients with MCL. The mean survival of patients with classic MCL has been estimated between 32 months and 56.3 months, while the mean survival of patients with BMCL is approximately 24 months (Lardelli *et al.*, 1990; Pittaluga *et al.*, 1995).

Although classic MCL has been described in the mucosal areas of the head and neck (including Waldeyer's ring) in varying proportions (Lardelli *et al.*, 1990; Menarguez *et al.*, 1994; Ott *et al.*, 1994; Fraga *et al.*, 1995; Norton *et al.*, 1995; Pittaluga *et al.*, 1995; Oka *et al.*, 1996; Weisenberger and Armitage, 1996; Zoldan *et al.*, 1996), the blastic variant of MCL has been specifically described in the mucosa of the head and neck only in the study of Norton and colleagues (one case in Waldeyer's ring) (Norton *et al.*, 1995) and more recently by Soslow *et al.* (one case in the oropharynx) (Soslow *et al.*, 1997). Mantle cell lymphoma is thought to terminate with blastic differentiation rather than in large cell (centroblastic) differentiation as occurs in other types of small B-cell lymphoma (Harris *et al.*, 1994). This speculation that blastic progression occurs in MCL has been supported by autopsy findings (Norton *et al.*, 1995; Weisenberger and Armitage, 1996). An anaplastic variant (AMCL) (Ott *et al.*, 1994), a large cell variant (LCMCL), (Zoldan *et al.*, 1996) as well as other variant forms of MCL have also been described (Swerdlow *et al.*, 1996). Similar to BMCL, both the anaplastic and large cell forms are described as having blast-like cells with finely dispersed chromatin, small indistinct nucleoli and little cytoplasm. However, the cellular components of LCMCL are described as larger than those of either MCL or BMCL (Zoldan *et al.*, 1996) while the cellular components of AMCL have a more heterogenous morphology than those of either the MCL or BMCL (Ott *et al.*, 1994). These variant forms, similar to BMCL, have short survival periods. All cases of AMCL that have been reported showed generalized dissemination during the course of the disease with aggressive clinical behaviour (Ott *et al.*, 1994 and 1996). Based on the presence of marked cytomorphological variability, but the absence of transformed cells or plasmacytoid differentiation, as well as a rapidly fatal clinical course, *Case 3* reported herein may represent an example of AMCL. However, we prefer to categorize this tumour within the spectrum of BMCL, similar to cases presented by Ott (Ott *et al.*, 1997) and Kaleem (Kaleem *et al.*, 1996).

The morphological differential diagnosis of BMCL occurring in nodal and in extranodal sites includes other lymphomas of both B- and T-cell types, especially lymphoblastic lymphoma, as well as nasopharyngeal undifferentiated carcinoma, small cell carcinoma with neuroendocrine differentiation, granulocytic sarcoma and other small round cell malignant tumours. Because of the therapeutic differences, these are important to distinguish. T-lymphoblastic lymphoma (T-LBL) can be readily distinguished from BMCL by the characteristic T-cell phenotype and expression of TdT. However, differentiation of BMCL from lymphoblastic lymphomas of B-cell phenotype (B-LBL) is more problematic. This issue was recently discussed by Cheng *et al.* (1994) and Soslow *et al.* (1997). Cheng reported three cases of *atypical* B-cell lymphoblastic lymphomas (B-LBL) in lymph node with clinical features that were felt to be unusual for B-lymphoblastic lymphomas, including occurrence in older patients a more favourable course (most of the B-LBL died within eight months whereas the *atypical* B-LBL were longer lived), bulky nodal disease and lack of extranodal involvement. Cheng *et al.* felt that these cases represented MCL (Cheng *et al.*, 1994), we feel that these probably represent BMCL. Of note is the *atypical* B-LBL expressed CD5 while the typical B-cell lymphoblastic lymphomas did not (Cheng *et al.*, 1994). Unfortunately, only one of our cases expressed CD5 in paraffin (Dorfman and Shahsafaei, 1997). TdT was not useful in distinguishing the B-LBL from the *atypical* LBL in the study of Cheng *et al.* (1994) but has proven useful in other studies (Soslow *et al.*, 1997). Although seen in none of Cheng's cases, peripheral blood involvement can be seen in MCL and BMCL further confusing the clinicopathological picture (Vadlamudi *et al.*, 1996). In the study of Soslow *et al.*, Bcl-1 (PRAD-1/cyclin D1) was useful in differentiating B-LBL and BMCL (Soslow *et al*, 1997). All of our cases showed positive Bcl-1 protein, which was helpful in the absence of CD5 immunoreactivity.

The differentiation of BMCL from types of non-Hodgkin's lymphomas, other than B-LBL, is also assisted by the presence or absence of cyclin D1 protein (de Boer *et al.*, 1995; Swerdlow *et al.*, 1995; Oka *et al.*, 1996). CD43/MT-1 and Bcl-2, a marker expressed in normal mantle cells, are also expressed in most BMCL (Lardelli *et al.*, 1990; Contos *et al.*, 1992; Fraga *et al.*, 1995; Weisenberger and Armitage, 1996). Cyclin D1 is overexpressed at the mRNA level as a result of a specific chromosomal rearrangement, t(11;14)(q13;q32), involving the BCL-1 locus on chromosome 11q13 and the immunoglobulin heavy chain gene complex on chromosome 14q32 (de Boer *et al.*, 1995). We confirmed that two of our cases were positive for t(11;14) at the major translocation cluster by PCR. While not pathognomonic for MCL, this translocation is highly specific for MCL (de Boer *et al.*, 1995; Oka *et al.*, 1996) and the protein product, Bcl-1/cyclin D1, has only rarely been found in other non-Hodgkin's lymphomas (Swerdlow *et al*, 1996). Further, cyclin D1 is more often over expressed in BMCL and variant forms than classic MCL (Norton *et al*, 1995; Segal *et al.*, 1995), possibly making BMCL easier than MCL to separate from other lymphomas. The differentiation of BMCL from nasopharyngeal undifferentiated carcinoma, small cell carcinoma from neuroendocrine differentiation and other small round cell malignant tumours is readily accomplished by immunohistochemistry (absence of lymphoid markers and the presence of epithelial, neuroendocrine and/or specific mesenchymal markers).

The cases in this study illustrate characteristics of BMCL which differentiate it from other types of blastic-appearing non-Hodgkin's lymphomas in the Waldeyer's ring. BMCL is found in older individuals with a male predominance, making it clinically distinct from other high grade lymphomas with a blastic appearance. Although, bone marrow and peripheral blood involvement can make BMCL difficult to distinguish from B-LBL, it should not preclude the diagnosis of BMCL.

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Address for correspondence:
Nadine S. Ives Aguilera, M.D.,
Department of Hematopathology,
AFIP,
Washington D.C., 20306-6000
USA

Fax: 202-782-9157
E-mail: aguilera@afip.osd.mil