# Angiotropic Lymphoma: An Immunophenotypically and Clinically Heterogeneous Lymphoma

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**Angiotropic lymphoma (AL) is an uncommon lymphoma often presenting with nonspecific clinical features and having a high mortality rate. Although not specifically recognized by the Revised European-American Classification of Lymphoid Neoplasms, it likely will appear as a subtype of diffuse large B-cell lymphoma in the upcoming WHO classification. Some authors may also consider it to be a subtype of cutaneous lymphomas. Recent studies have reported an immunophenotypic heterogeneity of AL, and in rare instances, an association with other NHL. To further characterize AL, we studied the immunophenotype by immunohistochemistry for CD5, CD10, CD20, bcl-2, and bcl-6 in 18 cases of B-cell AL identified at three medical centers in North America. Bcl-2 gene rearrangement status by polymerase chain reaction and Epstein Barr virus status by *in situ* hybridization also were evaluated.Eight men and 10 women were identified with AL (median age 71 years). Eleven patients were diagnosed in life and seven were diagnosed at autopsy. Neurologic symptoms were the most common presentation, seen in six patients. Skin was the most commonly biopsied site. All showed classic intravascular localization; in two cases, there was also a minor diffuse large cell lymphoma component observed in some organs. Most (89%) of the cases expressed bcl-2 protein; CD10, bcl-6 and CD5 were each expressed in 22% of cases. Based on CD5 and CD10 expression, three major groups were evident: CD5−, CD10− (11 cases); CD5+, CD10− (3 cases), and CD5−, CD10+ (3 cases). Even though a follicle center lymphoma preceded the AL in one patient, we did not detect bcl-2 gene rearrangement in any of these cases. All cases were negative for Epstein Barr virus. Of the five treated with chemotherapy, two achieved a complete remission.Based on these findings, we conclude that ALs are clinically and immunophenotypically heterogeneous and may represent more than one pathogenetic entity. In some instances AL may be preceded by another lymphoproliferative disorder, raising the possibility that some cases of AL may represent a transformation from another type of lymphoma. Cutaneous manifestations of AL are common; however, it appears to be a systemic lymphoma. Although often fatal, patients with AL who are diagnosed early and treated with chemotherapy may achieve remission.**

**KEY WORDS: Angiotropic, Autopsy, Immunophenotype, Immunohistochemistry, Lymphoma,**
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Angiotropic lymphoma (AL) was first described in 1959 by Pfleger and Tappeiner as *angioendotheliomatosis proliferans systemisata* and considered to be of endothelial origin (1–4). Ansell *et al.* (5)suggested a lymphoid origin in 1982 by demonstrating surface Ig on the neoplastic cells. Subsequently, Bhawan *et al.* (6) and Wrotnowski *et al.* (7) reported leukocyte common antigen expression in 1985. The lymphoid nature was confirmed by Wick *et al.* (8) in 1986. Since then, other studies have demonstrated B- and T-cell monoclonality in AL (9–12). Although not specifically recognized as an entity in the Revised European-American Classification of Lymphoid Neoplasms, the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma study group has proposed AL as a subtype of primary cutaneous lymphoma (13, 14). The WHO classification of lymphomas will probably recognize AL as a variant of diffuse large B-cell lymphoma (DLBCL) (15).

AL is characteristically confined to intravascular spaces, although extravascular involvement may


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occur (8, 14). It often involves multiple organs, but lymph nodes, spleen and bone marrow are generally spared; when these organs are involved, the pattern is diffuse rather than intravascular (16). Presenting features are nonspecific including mental status changes, skin lesions and fever; thus the diagnosis is often unsuspected and made at autopsy (17). The great majority of cases reported have been of B-cell lineage, with a few of T-cell lineage (12, 18–20). Expression of histiocytic markers, in the absence of B- and T-cell markers (21, 22) or clonal rearrangement has been reported in rare cases (21).

Recent studies of B-cell AL suggest the existence of distinct immunophenotypic groups (9, 11) and a relationship to follicle center lymphoma (FCL) (9, 23). The objective of this study was to characterize a relatively large number of B-cell AL to 1) describe the clinical features of these cases, and 2) determine whether distinct immunophenotypic patterns exist.

## MATERIALS AND METHODS

### Cases

A total of 18 B-cell AL cases from the Cleveland Clinic Foundation, Cleveland, Ohio (cases 1–6 and 16–18, 1986–2000), the City of Hope National Medical Center, Duarte, California (7–10, 1989–1997), and the Cross Cancer Center, Edmonton, Alberta (11–15, 1991–1998) were studied (Table 1). Of the 11 patients diagnosed in life, there was available follow up in eight. Autopsies were done in nine patients, with complete reports and slides available in five patients. Patients 1 to 3 and 18 have been reported previously (24–27).

### Immunohistochemistry and Molecular Studies

Paraffin immunohistochemistry for CD3 (Zymed, South San Francisco, CA, predilute), CD5 (Novocastra, New Castle upon Tyne, UK, 1:10), CD10 (Novocastra, 1:5), CD20 (DAKO, Carpinteria, CA, 1:50), cyclin D1 (Novocastra, 1:10), bcl-2 (Ventana Medical Systems, Tuscon, AZ, predilute) and bcl-6 (Santacruz Biotechnology, Santa Cruz, CA, 1:20) was performed (with appropriate controls) in all cases using an automated immunostainer (Ventana Medical Systems) (28).

Polymerase chain reaction (PCR) for the t(14;18) translocation was done using DNA extracted from paraffin-embedded tissues in Cases 1 to 6 and 11 to 18 with major breakpoint region primers according

**TABLE 1. Clinical and Immunophenotypic Features of 18 Patients with B-cell Angiotropic Lymphoma**

| Number | Age/Sex | Clinical History | Diagnostic Site | Treatment | Follow-Up | Immunophenotype |
|---|---|---|---|---|---|---|
| 1 | 69 F | Lower extremity weakness ×6 mo | Autopsy[a] | Steroids | — | CD20, Bcl-2 |
| 2 | 67 M | Lower extremity weakness ×7 mo | Sural nerve | Chemotherapy | ANED 9 mo | CD20, Bcl-2, CD10 |
| 3 | 46 F | Multiple episodes of sensorimotor deficits ×1 year | Autopsy[a] | Steroids | — | CD20, Bcl-2, CD5, CD10 |
| 4 | 72 F | Transient neurologic symptoms, seizures ×2 weeks | Brain, frontal lobe | Palliative | DOD 1 mo | CD20, Bcl-2 |
| 5 | 66 M | Pleural effusion, acute renal failure ×1 mo | Autopsy[a] | None | — | CD20, Bcl-2 |
| 6 | 79 F | Skin lesion | Skin, lower limb | Chemotherapy initially and at relapse | Relapse at 24 mo, ANED 30 mo | CD20, Bcl-2, CD5, Bcl-6 |
| 7 | 77 F | NA | Skin, lower limb | NA | NA | CD20, Bcl-2, CD5, Bcl-6 |
| 8 | 82 F | NA | Skin, abdomen | NA | NA | CD20, Bcl-2, Bcl-6 |
| 9 | 68 M | Anemia, thrombocytopenia | BM | NA | NA | CD20, Bcl-2 |
| 10 | 57 F | "Brain infarcts" | Autopsy[b] | None | — | CD20, Bcl-2 |
| 11 | 71 M | Fever, dyspnea ×3 mo | Autopsy[b] | None | — | CD20, Bcl-2, CD10 |
| 12 | 80 M | Multiorgan failure ×1 week | Autopsy[b] | None | — | CD20 |
| 13 | 71 F | Jaundice | Liver[b] | Chemotherapy | DOD 5 mo | CD20, Bcl-2 |
| 14 | 90 M | Urinary obstruction | Prostate | None | DWD 2 mo | CD20, Bcl-2, Bcl-6, CD5 |
| 15 | 63 F | NA | BM | None | DOD 13 mo | CD20, Bcl-2 |
| 16 | 62 M | Multiple febrile episodes ×10 mo | Autopsy[a] | Chemotherapy 4 months before death | DOD 14 mo after PB evaluation | CD10 |
| 17 | 71 F | Lower limb weakness ×3 mo | T10 vertebra[a] | Steroids | DOD 0.5 mo | CD20, Bcl-2 |
| 18 | 71 M | Multiple skin lesions ×9.75 years, hepatomegaly | Skin, liver | PUVA at presentation; chemotherapy at 3 relapses | Lost to follow-up 1 year after 4th relapse (9.75 yr) | CD20, Bcl-2 |

[a] Autopsies with complete report.

[b] Autopsies with incomplete report.

NA, not available; BM, bone marrow; PB, peripheral blood; DOD, died of disease; ANED, alive, no evidence of disease; AWD, alive with disease; PUVA, psoralens and ultraviolet light-A.

to previously published methods (28). Epstein Barr virus status by *in situ* hybridization (EBER-ISH) was done in all cases following established protocols (29). A poly dT probe was used to assess RNA integrity.

DNA was extracted from 5-micron paraffin sections of involved splenectomy and autopsy renal tissue from Patient 16 using the Qiagen tissue kit (Valencia, CA). Immunoglobulin heavy chain gene rearrangement (IgH) PCR studies were performed, as previously described (30), with the following primers sets directed against the framework III and the joining regions of the IgH gene: VLJHA 5'-CAC CTG AGG AGA CGG TGA CC-3'; FRIIIA 5'-ACA CGG C(C/T)(G/C) TGT ATT ACT GT-3'. The primers were labeled with fluorescent dyes (Applied Biosystems, Foster City, CA) and the PCR products were separated on the ABI 310 Genetic Analyzer (Applied Biosystems). The PCR products were size electrophoresed on a 15% polyacrylamide gel, and clonal bands were purified using the Qiaex kit (Qiagen). The purified DNA was sequenced by using the BigDye terminator sequencing system (Applied Biosystems).

## RESULTS (Table 1)

### Clinical

Of the 18 patients, eight were male (62–90 years) and 10 were female (46–82 years), with a median age of 71 and a mean of 70 years. The most common clinical features were neurologic (6 patients: 1–4, 10, 17) and cutaneous (4 patients: 6–8, 18). Less commonly patients presented with dyspnea, anemia, thrombocytopenia, fever, jaundice, hepatomegaly, multiorgan failure and urinary obstruction. Eleven patients were diagnosed in life and seven were diagnosed at autopsy. Of the patients diagnosed during life, the most frequently biopsied site was the skin (4). Other biopsied sites were liver (2, one of whom also had skin biopsies), bone marrow (2), brain, sural nerve, prostate, and vertebral body.

Regarding treatment, five patients were treated with chemotherapy, two (2, 6) of whom have been in complete remission 9 and 30 months post-therapy; two (16, 13) died at 4 and 5 months. Patient 18 survived for 9.75 years with recurrent skin lesions and multiple chemotherapy treatments, but was then lost to follow-up (slides from the initial diagnosis of "reactive angioendotheliomatosis" were not available for this study). Three patients (4, 14, and 15) who received no chemotherapy died at 1, 2, and 13 months after diagnosis. Three patients had no available follow-up. The remaining seven had AL diagnosed at autopsy. In 5 patients diagnosed at autopsy, symptoms were present 1 week to 14 months before death. The clinical data are summarized in Table 1.

### Histopathology

H&E sections in all cases demonstrated intravascular lymphoma that involved capillaries, veins, and small arterioles. The cells in each case were large with scant-to-moderate amounts of cytoplasm. The nuclei were usually round with open chromatin and multiple small nucleoli. Immunoblastic cells were not a prominent feature of these lymphomas. Representative cases are illustrated in Figures 1 and 2.

Complete autopsy results, available in five patients, showed widespread involvement of the brain, adrenals, kidneys and lungs in all patients, and of liver, pancreas, thyroid, parathyroid, spleen, lymph nodes, GI tract, heart, prostate, ovary and uterus in some patients (Table 2).

Three patients are discussed in detail because of their instructive features. Patient 16 presented with multiple febrile episodes. The white blood count was $10.4 \times 10^9$/L with 28% "atypical" lymphocytes. Unfortunately, the blood smear was not available for review. Flow cytometry demonstrated a CD19+, CD23+, CD5−, kappa light chain restricted population. A bone marrow biopsy showed a rare nonparatrabecular lymphoid aggregate of small and occasional large cells. This was interpreted as a low grade B-cell lymphoproliferative disorder and treatment was not considered at this time. A CD20 immunostain (performed for this study) showed small and occasional large B-cells in the aggregate and a rare sinusoid containing B-cells that was not visible on hematoxylin and eosin sections. His systemic symptoms worsened and splenomegaly became evident 10 months after initial presentation. A splenectomy was performed that revealed a diffuse proliferation of predominantly small lymphoid cells with condensed chromatin principally in the splenic red pulp and sinuses. Again, this was interpreted as a low-grade lymphoma. Despite this, the patient was treated with adriamycin-based multiagent chemotherapy but died 4 months later. At autopsy there was conventional B-cell AL in multiple organs including brain, kidney, adrenal, lymph nodes, GI tract, prostate and lung, with unequivocal cytologic features of a large cell lymphoma. Figure 3 illustrates the bone marrow, spleen, and kidney findings.

Patient 17 presented with a 3-month history of lower extremity weakness. The past medical history included carcinomas of the colon and breast 11 and 8 years before this time, respectively. MRI showed multiple nodules in the leptomeninges, vertebral bodies and nerve roots, clinically consistent with metastatic carcinoma. A 10th thoracic vertebral bi-

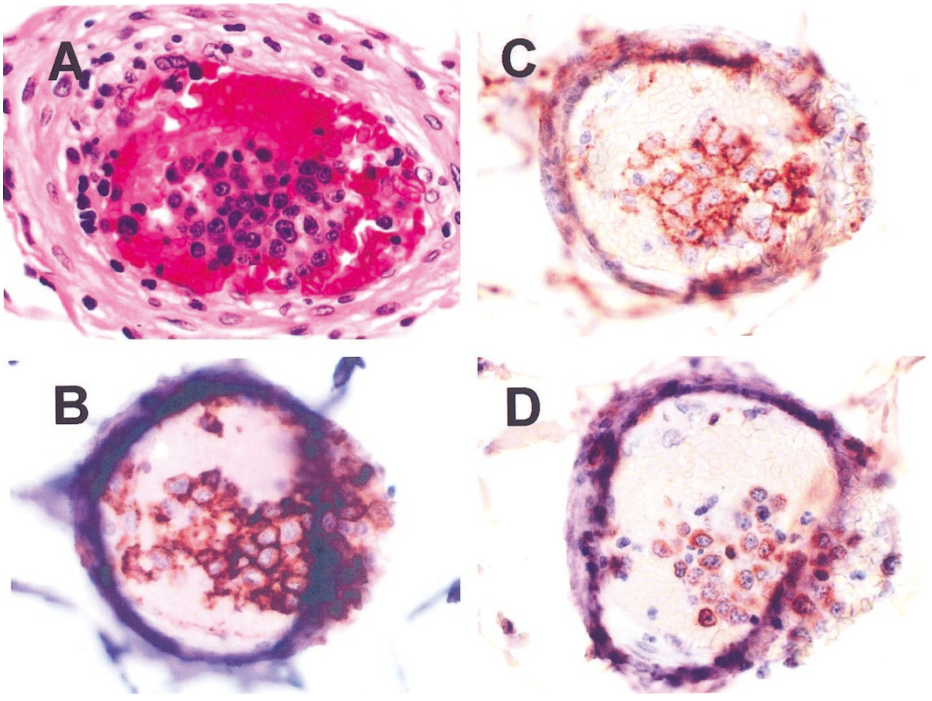


**FIGURE 1.** Case 2. Example of AL demonstrating a CD20+, CD10+, bcl-2+ phenotype. **A**, H&E; **B**, CD20 immunostain; **C**, CD10 immunostain; **D**, bcl-2 immunostain.

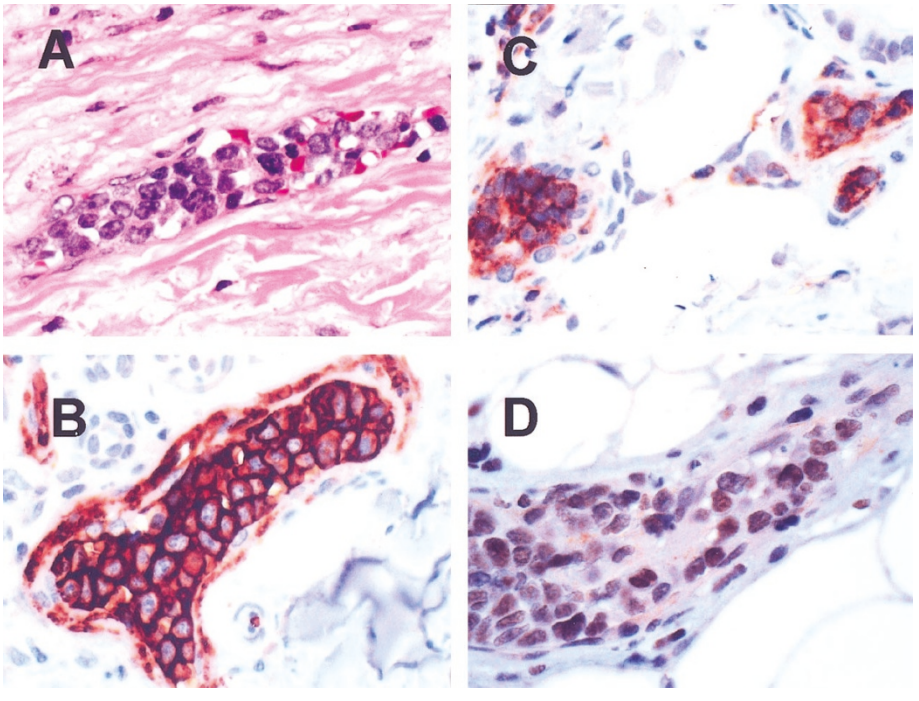


**FIGURE 2.** Case 7. Example of AL showing expression of CD20, CD5, and bcl-6. **A**, H&E; **B**, CD20 immunostain; **C**, CD5 immunostain; **D**, bcl-6 immunostain.

opsy showed an intravascular (minor) as well as an extravascular proliferation of intermediate to large atypical CD20+ B-cells. Chemotherapy was not an option because of her poor general condition and the patient died 2 weeks later. At autopsy there was multiorgan involvement by B-cell AL in the brain, kidney, adrenal, heart, and lung. In the left atrial subendocardium, a 2 × 1 cm nodule showing extravascular involvement was also found.

Patient 11 presented 21 months before death with a stage I FCL, grade 1. He was treated with local radiation and attained a complete remission.

**TABLE 2. Organ Involvement in Five Cases at Autopsy**

| Organ | Patient | | | | |
|---|---|---|---|---|---|
| | 1 | 3 | 5 | 16 | 17 |
| Brain | NE | + | + | + | + |
| Adrenal | + | + | + | + | + |
| Kidney | + | + | + | + | + |
| Lung | + | + | + | + | + |
| GU | + | + | + | + | − |
| GI | + | + | − | + | − |
| Heart | − | + | + | − | + |
| Liver | + | − | + | − | − |
| Pancreas | − | + | + | − | − |
| Spleen | − | − | + | +/−[a] | − |
| Lymph node | − | − | + | + | − |
| Thyroid/parathyroid | − | + | − | − | − |

[a] Involved at splenectomy during life (see Results).
NE, not examined.

Eighteen months later he developed unexplained fevers and dyspnea with a negative radiologic examination, bone marrow biopsy, and liver biopsy. He died 3 months later. Autopsy revealed multiorgan involvement by B-cell AL, without evidence of a recurrent FCL.

### Immunohistochemistry (Table 1)

All cases were negative for CD3 and cyclin D1; 17/18 expressed CD20. Case 16 was CD20, CD79a and CD3 negative, but expressed CD45RB. A B-cell lineage was assumed from the previous flow cytometric and genotypic studies (above). Sixteen (89%) cases expressed bcl-2. Ten (56%) cases were negative for CD5, CD10, and bcl-6 expression. Four cases (22%) each expressed CD5, bcl-6, and CD10. Bcl-6 and CD5 were coexpressed in three (17%) and, CD5 and CD10 in one case. No case coexpressed CD5, CD10 and Bcl-6.

### PCR, EBER-ISH, DNA Sequencing

The t(14;18) was not detected by PCR using major breakpoint region primers in the 14 cases tested (1–6, 11–18). All 18 cases were negative for EBER. PCR of the splenectomy and autopsy renal samples from Patient 16 for IgH gene rearrangement revealed identically sized (116 base pair) products, supporting identical clones in the different samples. DNA sequencing of these products showed identical sequences, confirming clonal identity.

## DISCUSSION

B-cell AL, a rare subset of DLBCL, often is diagnosed at autopsy because the clinical features are nonspecific. There is a notable absence of lymphadenopathy, splenomegaly or circulating lymphoma cells in the majority of cases. These factors contribute to a delayed diagnosis, misdiagnosis or both. The most common presenting features are neurologic, seen in approximately two-thirds of patients (31). Neurologic manifestations include progressive multifocal cerebrovascular events, spinal cord and nerve root vascular syndromes, subacute encephalopathy, and peripheral and cranial neuropathies (31). Cutaneous manifestations are also common and often consist of hyperpigmented or hemorrhagic lesions on the thighs and abdomen (31). However, patients can present with numerous other signs and symptoms, including fever, hepatomegaly, urinary obstruction, renal failure, adrenomegaly and dyspnea.

Most previous series of AL are relatively small (fewer than 10 cases) and detailed immunophenotypic features are lacking (8, 18, 31–35). To better characterize these cases and determine whether common immunophenotypic patterns can be discerned, we report a multicenter series of B-cell AL using paraffin-section immunohistochemistry for markers commonly used in lymphoma diagnosis. As seen in other large series, patients tended to be older adults with varied clinical presentations (31). The male to female ratio was 0.8, within the 0.7 to 5.0 range seen by others (8–10, 18, 31, 32, 35–37). Thirty-nine percent of our cases were not diagnosed until autopsy. Consistent with prior literature, common clinical findings were referable to neurologic and cutaneous involvement (31). However, other presentations occurred including cytopenias, organomegaly, jaundice, and urinary obstruction. All cases were B-cell lymphomas. A T-cell phenotype, although reported previously, was not seen (19, 20, 38–40).

In keeping with the systemic nature of AL, autopsies revealed involvement of brain, lung, kidney, and adrenal gland in all patients, while liver, pancreas, GI tract, spleen, lymph node, ovary, prostate, heart, thyroid, and parathyroid glands were less commonly involved (Table 2). This reflects the findings in the literature where brain (92–100%), kidney (17–100%), adrenal (33–79%), lung (33–100%), heart

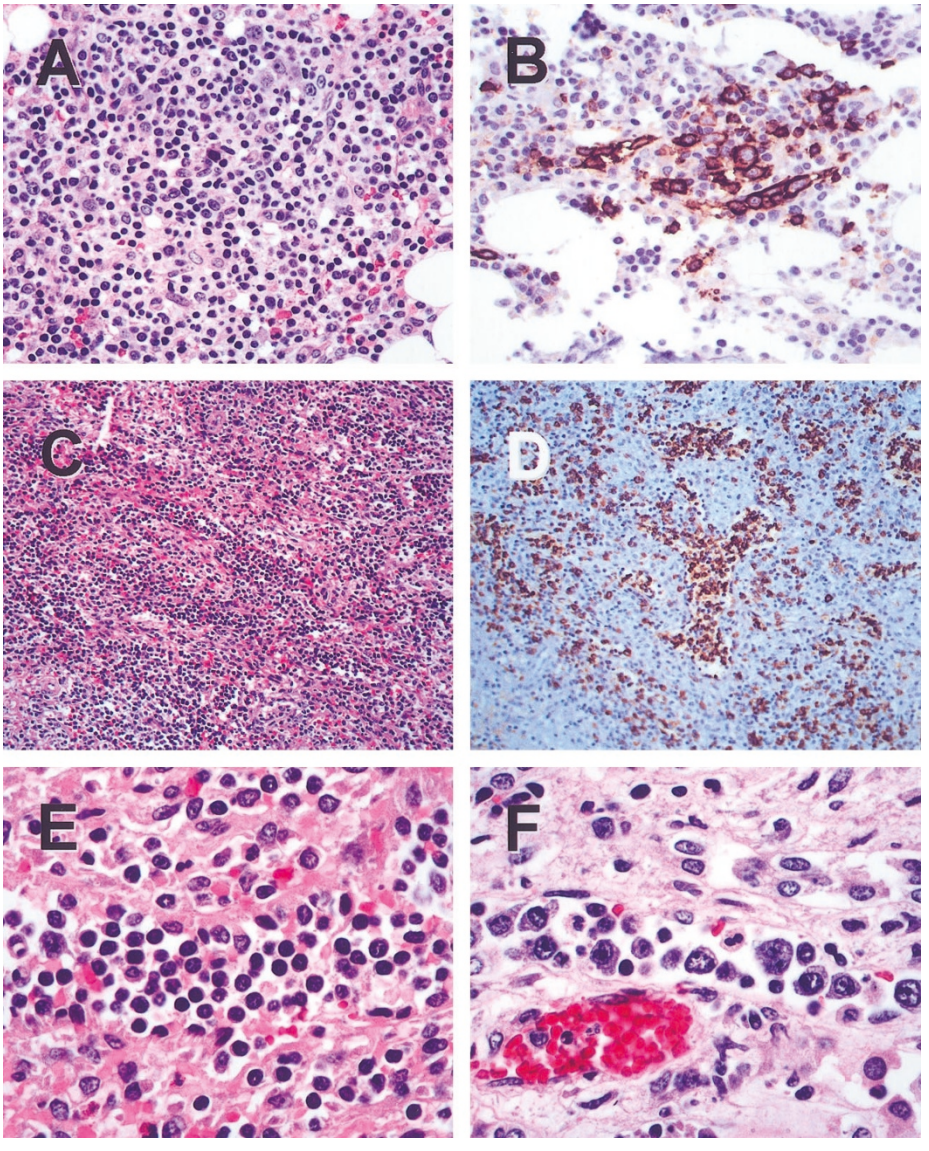


**FIGURE 3.** Case 16. **A**, Bone marrow during life showing a lymphoid aggregate of predominantly small cells. **B**, CD20 immunostain highlighting intrasinusoidal B-cells not readily apparent on H&E stain. **C**, H&E stain of splenectomy specimen showing red pulp infiltration by lymphoid cells. **D**, CD20 immunostain of spleen showing the sinusoidal distribution of the B-cells. **E**, High magnification of the splenectomy specimen demonstrating small lymphocytes within splenic sinusoids. **F**, Autopsy renal tissue showing AL at same magnification as **E**. The cells are transformed with vesicular chromatin and small nucleoli. Panels **E** and **F** are at identical magnification (1000×).

(17–64%), spleen (17–50%), lymph node (17–46%), liver (33–64%), GI tract (25–62%), and GU system (17–80%) showed evidence of AL (8, 31, 32).

The majority of cases expressed bcl-2 protein. This marker has been shown to be an indicator of poor prognosis in nodal DLBCL (41), in keeping with the poor prognosis of most patients with AL. However, the utility of bcl-2 expression in subtyping nodal NHL is limited (42). Bcl-6 protein is expressed in the vast majority of FCL but also appears to be present in a majority of DLBCL (43, 44). Only four of our AL cases expressed bcl-6 protein. Thus the percentage of AL cases expressing bcl-6 protein appears less than in typical DLBCL. The significance of this finding, if any, is unknown. Bcl-6 protein expression has been suggested to be a marker of germinal center origin (45, 46), but it does not appear to be specific (47, 48). In fact, the use of this protein expression status to predict a germinal center origin in large cell lymphomas has been called into question (43). A recent report by Zhang and colleagues suggests that low bcl-6 protein expression might be associated with a short disease-free survival in DLBCL (49). In our series of B-cell AL there appear to be no distinguishing features of the bcl-6 positive cases, although the number of cases is relatively small.

Regarding CD5 and CD10 expression, we saw a heterogeneous pattern that could be divided into three major groups, similar to other reports of DLBCL (9, 48). Group one (three cases: 2, 11, 16) includes the CD10+/CD5− lymphomas. Interest-

ingly, one of these cases occurred in a patient with a prior history of a FCL. Although we could not determine whether these two lymphomas had a common clonal origin, the expression of CD10 is consistent with the hypothesis that these are related to FCL. Previous reports (23) demonstrate that rare cases of AL can occur after FCL and may represent an unusual form of large cell transformation/progression. Group two (three cases: 6, 7, 14) was composed of CD5+/CD10− lymphomas. As suggested in *de novo* CD5-positive diffuse large cell lymphoma, these B-cell ALs may derive from a subset of CD5 expressing cells distinct from chronic lymphocytic leukemia or mantle cell lymphoma (9, 50). None of the patients in this study had a history of chronic lymphocytic leukemia or mantle cell lymphoma. Group three was the largest group and was comprised of the CD5-/CD10− cases (11), similar to the findings in non-angiotropic large B-cell lymphomas (48).

One case (Case 3) was unusual in that both CD5 and CD10 were expressed. In our experience with nodal large cell lymphomas using flow cytometry, this is unusual and the significance of this finding, if any, is unknown. It may represent a phenotypic aberrancy often seen in malignant cells, analogous to what is seen in acute leukemias (51). One recent report of the immunophenotype of diffuse B-cell lymphomas using flow cytometry noted a relatively high percentage of phenotypic aberrancy, including CD5 and CD10 coexpression (52). However, this does not appear to be the collective experience of others (13).

The t(14;18) seen in most FCL was not detected in any of the tested specimens using primers to the major breakpoint region. The sensitivity of our assay is approximately one in 10,000 cells. Thus, it appears that the majority of cases of AL are not related to FCL. However, we acknowledge the fact that we may indeed be missing cases with a t(14;18) because we did not analyze for the other breakpoints. In fact, the one case with a history of FCL was also negative; however, the original lymphoma was also negative for the translocation by PCR using major breakpoint region primers (data not shown). Likewise, Epstein Barr virus (EBV) was absent in our cases by EBER-ISH. This is in agreement with the series of Kanda *et al.* in which, although EBV was detected by PCR, EBER-ISH showed that the lymphoma cells were not the source of EBV (10). Similarly, Bergmann and colleagues did not detect EBV in their small series of central nervous system AL (53). EBV has been detected in AL but usually in immunocompromised patients or in T-cell AL (54–56).

Two points are worth emphasizing. First, B-cell AL can be associated with or preceded by a lymphoproliferative disorder (mostly large cell lymphoma) in up to one-third of cases (4–6, 23, 31, 56–58). It is uncertain whether the two lymphomas are related or not because clonality studies comparing them have not been performed. In one of our patients (17) there was an extravascular DLBCL diagnosed on vertebral biopsy; however, the predominant pattern almost everywhere else at autopsy was AL. On retrospective analysis, the diagnostic vertebral body biopsy did show a minor intravascular component. Because the patient died within 2 weeks, we believe that these two processes are the same. This, along with finding a focus of DLBCL in the heart at autopsy, would support considering AL as part of the spectrum of DLBCL, as is proposed in the upcoming WHO classification (15). Patient 16 carried a diagnosis of a CD5-negative low-grade lymphoproliferative disorder that was ill-defined. The bone marrow contained small B-cells as well as scattered large B-cells and was not clearly a DLBCL. The spleen was also difficult to classify. It contained an unusual red-pulp and sinusoidal distribution with predominantly small B-lymphocytes. The autopsy, however, demonstrated extensive AL with a more conventional large cell cytology. The finding of identical IgH rearrangements by PCR and sequencing favors the interpretation that these are manifestations of one and the same lymphoma, perhaps in the process of transforming from a low to high grade process over a period of 4 months. Of the low grade NHLs, FCL and gastric MALT-type lymphoma have been reported in rare patients with B-cell AL (23, 37). Case 11 had a grade I FCL 21 months before B-cell AL. Both lymphomas expressed bcl-2 and CD10 but not bcl-6. Both lacked bcl-2 gene rearrangement. Cases such as these raise the possibility that B-cell AL, in some instances, represents a transformation from a lower grade process and hint at a histogenetic diversity similar to that proposed for other lymphomas such as T-cell rich B-cell large cell lymphoma (59). Further studies must be done to definitively demonstrate clonal relatedness.

Second, although AL has a poor prognosis, some patients may respond to appropriate multiagent chemotherapy. DiGiuseppe and colleagues reported a series of 10 patients with AL, four of whom were treated with combination chemotherapy with encouraging results (18). These authors also review numerous prior studies demonstrating a complete remission rate of 43%. More recently Calamia and colleagues and Kanda *et al.* report a favorable response to chemotherapy (10, 60). Autologous bone marrow transplantation (at relapse) has also been successful in a single case report (61). In our series, two of the five patients (2, 6) treated with chemotherapy achieved a complete remission. One is alive without disease at 30 months having been treated for a relapse. Patient 18 illustrates that multiple

relapses can be successfully managed with chemotherapy. Thus, AL patients, when treated early and aggressively have the potential for achieving a durable remission. As suggested by Bogomolski-Yahalom *et al.*, we agree that it is unknown whether the poor survival of AL is due to the failure to diagnose and properly treat patients or due to biologic features intrinsic to this unusual type of lymphoma (57). Some clues to the pathogenesis and biologic behavior of this lymphoma may be found by further study of adhesion molecule expression (10, 32, 37, 39). Despite the generally recognized aggressive clinical behavior of AL, it appears that a prolonged course can occur, as demonstrated by Patient 18 (35, 62).

In summary, B-cell AL is a heterogeneous disorder with a myriad of clinical presentations. There continues to be a high mortality; however, treatment successes do occur with multiagent chemotherapy. Patients may have pre-existing or coexisting lymphoproliferative disorders raising the possibility that, at least in some cases, AL is a transformation of a lower grade process, confirmed by sequencing in one of our cases. EBV infection appears to play no role in this lymphoma. Although most cases express bcl-2 protein, they lack the t(14; 18). Immunophenotypically, these cases are also heterogeneous and can be divided into three major groups based on CD5 and CD10 expression. The significance of such a division is uncertain but may have relevance as more is learned regarding the pathogenesis of this unusual form of lymphoma. The above findings seem to suggest that, at this time, AL may not be a single discrete entity with a single pathogenetic, phenotypic, and molecular genetic profile (much like DLBCL). Despite the inadequacies of evolving classification systems, AL does occur and clinicians and pathologists must be aware of AL to make earlier diagnoses.

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