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The Variable MR Appearance of Primary Lymphoma of the Central Nervous System: Comparison with Histopathologic Features

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PURPOSE: To describe the MR features of primary central nervous system (CNS) lymphoma and to determine whether there is a correlation with histopathologic findings. **METHODS**: The MR images, pathologic specimens, and clinical records of 23 patients with primary CNS lymphoma were reviewed. The imaging and pathologic characteristics were tabulated and compared by using the standard tests for association in a two-dimensional contingency table. RESULTS: A total of 61 lesions were present in 23 patients; 12 patients (52%) had multiple lesions. All lesions were isointense or hypointense on T1-weighted images, and 53% were isointense or hypointense on T2-weighted images. Twenty patients received intravenous contrast material, and 43 (91%) of 47 lesions enhanced. The three patients who had nonenhancing lesions received steroids before the initial MR studies. Enhancement patterns differed between the immunocompetent and the immunocompromised hosts, with the latter group harboring a higher percentage of rim-enhancing lesions. Twenty-seven (44%) of the lesions were centered in a cerebral hemisphere and 14 (23%) were centered in the central gray matter. There was a statistically significant correlation between a higher degree of necrosis histologically and hyperintensity on T2-weighted MR images. The degree of necrosis also showed a positive correlation with rim enhancement. CONCLUSIONS: Primary CNS lymphoma has a variable MR appearance that correlates with the severity of intratumoral necrosis. These imaging characteristics, as well as lesion location, mean lesion size, and proclivity to harbor necrosis, are altered in the immunocompromised host.

Index terms: Brain neoplasms, magnetic resonance; Lymphoma

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Primary central nervous system (CNS) lymphoma is an aggressive neoplasm with an indeterminate pathogenesis. It is increasing in frequency in both immunocompetent and im-

AJNR 18:563–572, Mar 1997 0195-6108/97/1803–0563 © American Society of Neuroradiology munocompromised patients, and currently represents 0.2% to 2.0% of primary malignant lesions of the CNS (1-9). Primary CNS lymphoma is virtually always the non-Hodgkin type, and the vast majority are B-cell lymphomas. Primary T-cell lymphomas in the CNS have been reported, but they are rare (11, 12). Primary CNS lymphoma is histologically identical to systemic extranodal non-Hodgkin lymphoma, and may thus be categorized according to the working formulation for the classification of non-Hodgkin lymphomas (13). Previous investigators have evaluated the computed tomographic (CT) characteristics of primary CNS lymphoma (6, 14-16) and their correlation with the histopathologic features (4, 17). The magnetic resonance (MR) imaging features have also been reported (7, 8, 14, 18). The purpose of this article is to describe the MR features of primary CNS lymphoma and to de-

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termine any correlation with the histopathologic findings.

Materials and Methods

The MR images, histologic specimens, and clinical records of 23 patients with pathologically proved primary CNS lymphoma were reviewed. All specimens were obtained via open or stereotactic needle biopsy. Spin-echo MR imaging was performed on a 1.5-T unit. T1-weighted spin-echo axial and sagittal, 600/20/1 (repetition time [TR]/echo time [TE]/excitations), and long-TR dual-echo axial sequences (2500/30,90/1) were obtained. Other parameters included a 21-cm field of view, a 256 \times 192 matrix, and 5-mm-thick sections. Contrast-enhanced T1-weighted axial images were obtained after intravenous administration of 0.1 mmol/kg gadopentetate dimeglumine.

The imaging studies were evaluated for the number, location, and size of the lesions by two neuroradiologists who were blinded to the patients' clinical history and histologic findings. In addition, MR signal characteristics of each lesion were evaluated on T1- and T2-weighted images and rated as hyperintense, isointense, or hypointense relative to gray matter. The pattern of enhancement was categorized as solid, rim(ring)-like, or irregular. The degree of mass effect and perifocal white matter signal changes (edema) were graded as low, moderate, or high. The contour of the lesion was also noted (smooth, lobular, or irregular). Finally, the location of each lesion was documented and assessed for contiguity with an ependymal or meningeal surface.

The pathologic slides were reviewed by a neuropathologist using light microscopy. The tumors were classified according to the working formulation of malignant lymphomas (13). The specimens were also evaluated for the degree of tumor cellularity and necrosis. Some of the biopsy specimens included adjacent brain parenchyma. These were evaluated for the presence of perifocal edema and glial response. The relative degree or severity of each of these features was graded as low, moderate, or high. A comparison of all specimens in this trial and extensive experience with CNS neoplasms provided the basis for the semiquantitative analysis performed by the neuropathologist. Because no universally accepted criteria for quantifying the degree of necrosis, edema, or cellularity are available, the relative severity of these parameters was used for analysis.

The imaging and pathologic characteristics were tabulated and compared by using the standard tests for association in a two-dimensional contingency table. Each of the MR characteristics (signal intensity, enhancement pattern, white matter change, mass effect, and lesion contour) was compared with each of the pathologic features (histologic subtype, cellularity, necrosis, edema, and glial response).

Results

Patients

The patients consisted of 14 men and nine women, 20 to 80 years old (mean, 57 years). Five of the men were positive for the human immunodeficiency virus and had acquired immunodeficiency syndrome (AIDS) (age range, 20 to 36 years; mean, 30 years). Nine men and nine women comprised the immunocompetent cohort; their ages ranged from 40 to 80 years (mean, 65 years).

Imaging

A total of 61 lesions were present in the 23 patients. Multiple lesions were present in 12 patients (52%). Three (60%) of the five AIDS patients had multiple lesions, with an average of 3.2 lesions per patient. Nine (50%) of the 18 immunocompetent patients had multiple lesions, with an average of 2.5 lesions per patient. Twenty patients received intravenous contrast material, which produced enhancement in 43 (91%) of 47 lesions. The three patients with the four nonenhancing lesions received steroids before the initial MR study (Fig 1). All the lesions for which a biopsy was done showed enhancement. In the immunocompetent cohort, 25 lesions (74%) showed a homogeneous enhancement pattern, one (3%) showed rim enhancement, four (12%) enhanced in an irregular pattern, and four (12%) did not enhance. All lesions in the AIDS patients enhanced: six (46%) with homogeneous enhancement, six (46%) with rim enhancement, and one (8%) with an irregular enhancement pattern. All lesions were isointense or hypointense on the T1weighted images relative to gray matter, and 53% were isointense or hypointense on the T2weighted images. The remaining 47% were hyperintense. Twenty-seven (45%) of the lesions were centered within a cerebral hemisphere, and 14 (23%) were centered in the central gray matter. Intraventricular, cerebellar, and brain stem lesions were less common (Table 1). Seventeen lesions (28%) abutted an ependymal surface; only five (8%) were contiguous with a meningeal surface. Hemispheric lesions were more prevalent in the AIDS patients (Table 1), and were more often contiguous with an ependymal (38%) or meningeal (13%) surface. The mean lesion size (largest diameter) for the



TABLE 1: Lesion location

Location	Immunocompetent Patients (%)		AIDS Patients (%)		Total (%)	
Hemisphere	16	(35)	11	(69)	27	(44)
Central gray	11	(24)	3	(27)	14	(23)
Corpus callosum	3	(7)	0		3	(5)
Intraventricular	3	(7)	1	(6)	4	(7)
Cerebellum	8	(18)	0		8	(13)
Brain stem	4	(9)	1	(6)	5	(8)
Total	45	(100)	16	(100)	61	(100)

immunocompetent group was 2.13 cm (range, 0.9 to 5.0 cm). This was larger than that seen in the AIDS cohort (mean, 1.64 cm; range, 0.8 to 3.0 cm).

Pathologic Findings

The histologic subtypes encountered were, in decreasing order of frequency, diffuse large cell (n = 13), immunoblastic (n = 4), small cleaved cell (n = 2), small lymphocytic (n = 2), and diffuse mixed cell (n = 2). The AIDS patients had only diffuse large cell or immunoblastic subtypes. Other histologic features are summarized in Table 2. The degree of perifocal edema and gliotic response could not be assessed in seven specimens because there was no brain parenchyma adjacent to the tumor as sampled. All patients with a moderate to high degree of necrosis histologically had intermediate-grade (diffuse large cell) (n = 5) or diffuse mixed cell (n = 1) or high-grade (immunoblastic) (n = 4)lymphoma.

Radiologic-Pathologic Correlation

Pearson's χ^2 test for association between the MR features and the histologic findings revealed a statistically significant correlation between a high degree of necrosis and hyperintensity on T2-weighted MR images (Table 3). Tumors with no or low necrosis were most commonly isointense to hypointense on T2-weighted images (Fig 2), and those with moderate to severe necrosis were more often hyperintense (Fig 3). The degree of necrosis also correlated with the pattern of enhancement (Table 4). Tumors with no or mild necrosis on light microscopy showed a statistically significant propensity to enhance in a solid pattern (Fig 4), whereas those with moderate to severe necrosis generally showed an irregular or rim-enhancing pattern (Fig 5). All AIDS patients had lesions that contained either moderate or severe necrosis, and rimenhancing lesions were much more common in this group (Table 5). We found no statistically significant correlation between the MR features and degree of cellularity, edema, or adjacent glial response on the corresponding histologic specimen.

Discussion

The mean age of 57 years in our cohort is comparable to that of other reported series of patients with primary CNS lymphoma (4, 5, 7, 19). As expected, the immunocompromised patients had a significantly lower mean age (32 years) than that of the immunocompetent cohort (65 years). The earlier age at presentation

Fig 1. Case 13: 61-year-old immunocompetent woman with diffuse large cell lymphoma.

A, Contrast-enhanced axial T1weighted image shows an enhancing lesion adjacent to the posterior aspect of the left lateral ventricle. Motion artifact causes some image compromise.

B, Axial T2-weighted image shows T2 prolongation in the distribution of the enhancing lesion. Additional hyperintense lesions are present in the contralateral hemisphere (*arrows*) spanning the genu of the corpus callosum.

Patient Age, y/Sex	Histology	Cellularity	Necrosis	Edema	Glial Response	No. of Lesions	MR Imaging*			
							T1-	T2-	Enhancement	
								Weighted	Weighted	Pattern
Immuno	competer	nt Patients								
2	43/M	Diffuse large cell	High	Low	High	High	3	lso	lso	Solid
3	80/M	Immunoblastic	High	High			1	lso	Нуро	Rim
4	75/F	Small lymphocytic	Low	None	Moderate	Low	3	Нуро	Hyper	Solid
5	66/F	Diffuse large cell	High	None			1	Нуро	Нуро	Solid
6	68/M	Small cleaved cell	Moderate	Low	Moderate	High	1	lso	Iso	Solid
7	67/M	Small cleaved cell	High	Low			1	Нуро	Нуро	Solid
8	55/M	Diffuse large cell	High	Low			6	Нуро		Solid
10	72/M	Diffuse large cell	Low	Low	Low	Low	3			
11	66/F	Diffuse large cell	High	None			1	Нуро	Нуро	Solid
12	50/M	Diffuse mixed cell	High	Low	Low	Low	1	Нуро	lso	Solid
13	61/F	Diffuse large cell	Moderate	None	High	Low	2	Нуро	Hyper	Solid
14	80/F	Diffuse mixed cell	High	High	Low	Low	2	lso	Hyper	Solid
16	75/M	Small	Low	None	Low	Moderate	5			Solid
		lymphocytic								
18	58/F	Diffuse large cell	Moderate	High	High	Moderate	1	Нуро	Нуро	Rim
19	74/F	Diffuse large cell	High	Low			5	Iso	Iso	Solid
20	40/M	Immunoblastic	Low	High	High	High	1			Solid
22	67/F	Diffuse large cell	High	High			1	Нуро	Нуро	Solid
23	69/F	Diffuse large cell	Moderate	Low	Moderate	High	6	Нуро	Hyper	Irregular
Immuno	compron	nised Patients								
1	36/M	Immunoblastic	Moderate	Hiah	Moderate	Moderate	5	Нуро	Hyper	Rim
9	20/M	Diffuse large cell	High	High	Low	Low	6	Нуро		Rim
15	33/M	Diffuse large cell	Moderate	High	High	Moderate	1	Нуро	Hyper	Rim
17	31/M	Diffuse large cell	Low	Moderate	High	High	1	Нуро	Нуро	Rim
21	31/M	Immunoblastic	Moderate	Moderate	Low	Low	3	Нуро	Hyper	

* Enhancement pattern and signal characteristics of dominant lesion. For statistical analysis, each lesion was assessed and tabulated. Iso indicates isointense; hypo, hypointense; and hyper, hyperintense.

for immunocompromised patients harboring CNS lymphoma manifests in a lower mean age reported in other series of AIDS patients with CNS lymphoma (8, 17). A male predominance in cases of primary CNS lymphoma is generally recognized (1–4, 7, 9, 19, 20). Our series also had a male preponderance; all the AIDS patients were males. However, the male-to-female ratio was equal in the immunocompetent group.

The CT features of primary CNS lymphoma are well documented (4–6, 16, 17). The MR features have also been described (7, 8, 14, 18). Early observations indicated that primary CNS lymphoma has signal characteristics similar to those of other intracranial neoplasms: T1 and T2 prolongation resulting in a hypointense appearance on T1-weighted images and a hyperintense appearance on T2-weighted images. Others have described primary CNS lymphoma as intracranial masses that are isointense with gray matter on long-TR images (7, 8). A hypointense appearance (relative to gray matter) has also been described (14). We also noted the absence of T2 prolongation in a significant number of lesions. In fact, a majority of the lesions (53%) were either isointense (33%) or hypointense (20%) relative to gray matter on T2-weighted images. This feature distinguishes primary CNS lymphoma from most brain tumors, which are generally hyperintense unless hemorrhage, calcification, or melanin is present.

Most lesions (91%) identified on long-TR images enhanced after administration of contrast material. Because the patients with nonenhancing lesions had received steroid therapy, a spurious reduction of the percentage of lesions that enhance is likely. A high prevalence of enhancement is consistent with other series, which range from 92% to 100% (3, 5, 7).

The pattern of enhancement seen in our series is also comparable to reported data, with 74% of lesions in the immunocompetent cohort showing homogeneous enhancement (7, 17). А

TABLE 3: Signal intensity on T2-weighted images versus degree of histologic necrosis

Degree of Necrosis	Signal Intensity on T2-Weighted Images (Relative to Gray Matter)			
	Hypoisointense	Hyperintense		
None to low	12	5		
Moderate to high	8	13		
	P	= .0461		

TABLE 4: MR enhancement pattern versus degree of histologic necrosis

Degree of Neerosia	Enhancement Pattern			
Degree of Recrosis	Solid	Rim/Irregular		
None to low	20	3		
Moderate to high	10	14		
		<i>P</i> = .0012		

Fig 2. Case 6: 68-year-old immunocompetent man with small cleaved cell lymphoma. Biopsy specimen showed minimal necrosis.

A, Contrast-enhanced axial T1weighted image shows a homogeneously enhancing lobular mass in the left frontal lobe.

B, Axial T2-weighted image depicts the lesion as relatively isointense with gray matter. The lesion contrasts sharply with the adjacent hyperintense vasogenic edema. Periventricular white matter changes, present posteriorly in both hemispheres and lateral to the right caudate head, are consistent with small-vessel ischemic changes (*arrows*).



Fig 3. Case 14: 80-year-old immunocompetent woman with diffuse mixed cell lymphoma.

B

A, Contrast-enhanced axial T1-weighted image shows the irregular contour of the enhancing mass adjacent to the left lateral ventricle. The mass extends into the splenium of the corpus callosum.

B, Axial intermediate-weighted image depicts the lesion as hyperintense relative to gray matter (*arrows*). This patient also has significant small-vessel ischemic disease involving the periventricular white matter.

C, Pathologic specimen shows a heterogeneous cell population with variable cellular size and shape. The large nuclei have a vesicular chromatin pattern and contain marginated nucleoli (*straight arrow*). There are areas of extensive necrosis (*curved arrows*) and densely cellular components (*open arrows*) within the tumor. The adjacent brain parenchyma (*not shown*) displayed no significant edema or gliotic response.









В

Fig 4. Case 12: 50-year-old immunocompetent man with diffuse mixed cell lymphoma.

A, Axial T1-weighted images reveal a hypointense mass in the right posterior frontal lobe. A slightly hyperintense margin delimits the lesion from adjacent vasogenic edema (*arrows*).

B, Contrast-enhanced axial T1-weighted image shows uniform, intense enhancement of the lesion.

Intermediate-weighted (C) and T2-weighted (D) images show mild perifocal edema and a slightly heterogeneous appearance of the lesion, which is relatively isointense with gray matter.

E, Photomicrograph of the pathologic specimen shows a diffuse proliferation of pleomorphic noncohesive cells in a neurofibrillary matrix. The variation in cell size is characteristic of mixed cell lymphoma. Several hyperchromatic nuclei are evident. There is a paucity of necrosis.









Fig 5. Case 3: 80-year-old immunocompetent man with immunoblastic lymphoma. Biopsy specimen revealed prominent necrosis.

A, Sagittal T1-weighted image shows a dilated (trapped) temporal horn (*small arrows*). The lesion (*open arrow*) is immediately posterior and superior to the ventricle and is not well demarcated from the adjacent edematous white matter.

Contrast-enhanced sagittal (B) and axial (C) T1-weighted images delineate the rim-enhancing lesion with a focal nodular component.

Intermediate-weighted (D) and T2weighted (E) images reveal extensive perifocal edema and a dilated temporal horn (open arrow) ventral to the lesion (*straight arrow*). The tumor is predominately hy-

pointense, with a hyperintense focus anteriorly (*curved arrow*). Histologically, this lesion had areas of high cellularity and a high degree of necrosis (Table 1), which may explain the hypointense and hyperintense foci on MR images, respectively.

TABLE 5: Imaging findings: enhancement patterns

Pattern of Enhancement	Immunocompetent (%)	AIDS Patients (%)	Total (%)
Solid	25 (74)	6 (46)	31 (66)
Rim	1 (3)	6 (46)	7 (15)
Irregular	4 (12)	1 (8)	5 (11)
None	4 (12)	0	4 (9)
Total enhancing	30 (88)	13 (100)	43 (91)

The frequency of rim enhancement in such patients before treatment is much lower (17), and was seen in only 12% of lesions in our series. In immunocompromised patients, rim enhancement was much more common (Fig 6). This pattern of enhancement was seen in approximately half the lesions in our immunocompromised patients, which is similar to the experience of other investigators (6, 15–17). Although characteristic, rim enhancement is not a distinguishing feature for lesions in either population. The primary differential considerations based on enhancement pattern include other neoplasms and infection.

In our series, lesion size (in largest diameter) tended to be smaller in AIDS patients (mean diameter, 1.6 cm; range, 0.8 to 3.0 cm) than in the immunocompetent group (mean diameter, 2.1 cm; range, 0.9 to 5.0 cm). Although some workers have noted this trend toward smaller lesions in immunocompromised patients (8), others have noted a tendency toward larger lesions in AIDS patients with primary CNS lymphoma (4, 18).

Overall, 52% of patients in our series had multiple lesions. In the immunocompetent group, 50% had more than one lesion. This is at the high end of reported values for multiplicity, which range from 11% to 50% (2–5, 7, 9, 19,





D

Fig 6. Case 17: 31-year-old AIDS patient with diffuse large cell lymphoma. Biopsy specimen revealed moderate necrosis.

Noncontrast (A) and contrast-enhanced (B) axial T1-weighted images reveal an irregular rim-enhancing lesion in the right dorsolateral pons and middle cerebellar peduncle.

Intermediate-weighted (*C*) and T2-weighted (*D*) images depict significant edema extending from the hypointense lesion (*arrows*).

20). The higher rate of multiplicity displayed in the AIDS cohort (60%) is congruent with the results of other researchers, who reported multiplicity rates ranging from 41% to 81% (14-16).

Almost half (45%) the lesions in this study were located peripherally within the hemispheres. Several authors report this as the most frequent location, with 46% to 50% of lesions so located (4, 5, 16, 19). The central gray matter is a characteristic location for primary CNS lymphoma, albeit not the most frequent. Only 23% of lesions in our series were located in the deep gray matter structures. This is only slightly higher than the 18% prevalence reported by Jellinger et al (19) and lower than that reported by Jack et al in two series, in which there was a 30% (5) and a 33% (4) prevalence of lesions in the central gray matter. Intraventricular and posterior fossa lesions were less common.

Contact with an ependymal or meningeal surface is another putative characteristic feature of primary CNS lymphoma, reported in as many as 75% of lesions (4). Roman-Goldstein et al (7) reported 58% abutting the ventricular system. This feature was less common in our series; only 28% of lesions were contiguous with an ependymal surface, and 8% with the meninges. Contiguity with an ependymal surface was more common in AIDS patients (38%) than in immunocompetent patients (24%) in our trial.

We used the working formulation for lymphomas to classify cases in our study and found low-, intermediate-, and high-grade subtypes. All of the AIDS patients with primary CNS lymphoma reviewed by Cordoliani et al (18) were found to have intermediate- to high-grade subtypes. This was our experience as well. None of the AIDS patients in our series had low-grade lymphomas according to the working formulation, and only four (22%) of the 18 immunocompetent patients did. Diffuse large cell lymphoma was the most frequent histologic subtype in our series (Table 2). Previous studies cite a similar experience (4, 7, 9, 17), while others show immunoblastic lymphoma as the most common (3, 20) subtype. Immunoblastic lymphoma was the subtype in all the patients with primary CNS lymphoma reported by Loureiro et al (21). In our AIDS cohort, the immunoblastic subtype was present in 40% of the patients, while 60% were diffuse large cell lymphomas.

Lesions harbored by patients in the AIDS cohort tended to show a higher degree of necrosis. The four immunocompetent patients in our study with lesions that showed a high degree of necrosis had immunoblastic (n = 2), diffuse mixed cell (n = 1), and large cell (n = 1) subtypes. The other patients had lesions that showed no or mild necrosis. Conversely, all the AIDS patients had lesions that showed moderate or severe necrosis. This is similar to the experience of Lee and coworkers (17), who noted a paucity of necrosis in the lesions they examined, except for those in the AIDS patients.

Similar to the experience of Jack et al (5), we found no imaging correlation with the pathologic subtype of primary CNS lymphoma. Our analysis of the other histologic characteristics for correlation with imaging features revealed a significant association between the degree of necrosis and two of the imaging parameters: the T2 signal intensity and the pattern of enhancement on contrast-enhanced T1-weighted images.

High signal intensity is expected with necrosis. In the absence of a significant degree of necrosis, primary CNS lymphoma tends to be isointense to hypointense relative to brain on long-TR sequences. This may be due to the high nuclear-to-cytoplasmic ratio and dense cellularity evidenced by these tumors. The MR features produced by such a lesion are obviously altered when necrosis is present, which then dominates MR contrast.

Likewise, the more characteristic homogeneous enhancement pattern would predictably be disrupted when necrotic debris replaces tumor centrally. In the setting of central necrosis, enhancement of the peripheral viable tumor surrounding central nonenhancing necrotic debris produces a ring-enhancing pattern.

Because this was a retrospective study, the biopsy method was not standardized. Some of the patients underwent open biopsy (n = 8), but a majority had needle biopsy (n = 15). In addition, while all lesions were evaluated on the imaging studies, not all lesions were subjected

to biopsy. Although most lesions in a given patient displayed similar imaging characteristics, the biopsy specimen obtained may not fully reflect the histologic features either of that lesion or of all lesions in that patient. Because all the lesions identified on MR images were included in the statistical analysis, it is important to consider that not all were confirmed pathologically. In addition, the pathologic and radiologic features were graded in a relative fashion, as no universally accepted scale for quantification is available. This introduces subjectivity into the assessment of the various parameters. However, our goal was not to provide quantification of the various features we evaluated but to look for correlations. A relative grading of the severity of each feature was thus deemed acceptable.

Neuroimagers should be aware of the variable MR appearance and distribution of primary CNS lymphomas within the brain. These tumors may be hyperintense, isointense, or hypointense relative to brain on T2-weighted images. The enhancement pattern is variable. Lesions are commonly multiple, hemispheric in location, and tend to enhance homogeneously in the immunocompetent host. In AIDS patients, primary CNS lymphoma is even more likely to present with multiple lesions. Rim enhancement is much more prevalent in these patients, a feature that is most likely due to the high degree of necrosis. The severity of necrosis on the histologic specimen had a significant correlation with the MR signal characteristics on T2weighted images and with the pattern of enhancement. Familiarity with these features should provoke consideration of primary CNS lymphoma when such lesions are encountered. This may prompt early biopsy rather than conservative management in the appropriate clinical setting.

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