PRIMARY CHOROIDAL MALIGNANT LYMPHOMA: REPORT OF A CASE AND REVIEW OF LITERATURE

F. Asadi Amoli*, M. Taher-Rajabi, M. R. Esfahani and A. Sadeghi

Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract- Non-Hodgkin lymphoma (NHL) is one of the masquerade syndromes of malignant melanoma that can occur with two main patterns of presentations in the eye: metastatic involvement of uveal tract, and primary involvement of retina. We report ophthalmic, imaging and histopathological findings in the first case diagnosed as primary choroidal NHL without central nervous system or systemic involvement. A 37-year-old woman presented with the complaint of severe visual loss in her right eye. Significant ocular finding included light perception of vision (LP), 2+ APD, 2+ cells in vitreous and intraocular pressure of 46 mmHg. Fundoscopic examination revealed exudative retinal detachment. Ocular echography showed choroidal thickening in addition to retinal detachment. MRI showed semilunar shape lesion in the posterior right globe suggesting choroidal melanoma. Systemic work-up could not reveal any underlying cause. The patient underwent enucleation with clinical suggestion of choroidal melanoma. Result of histological examination showed NHL (diffuse large B-cell type) of choroid. Immunohistochemical staining showed negative staining for HMB-45 and CD3, positive staining for LCA, and CD20. Multiple periodic lumbar puncture, bone marrow biopsies and MRI were unremarkable. No recurrence of tumor in systemic work-up was noted during the 36-months follow-up. Primary choroidal NHL is one of the causes of generalized thickening of choroid and should be considered in differential diagnosis of malignant melanoma. It is recommended to perform fine needle biopsy before performing surgery in any patient who has had an atypical malignant melanoma. This is, so far as we know, the first case diagnosed as primary choroidal NHL.

Acta Medica Iranica, 44(2): 145-150; 2006

Kay words: Choroidal tumor, choroidal malignant lymphoma, intraocular malignant lymphoma, primary intraocular lymphoma

INTRODUCTION

Pseudomelanomas or masquerade syndromes of melanoma are lesions that mimic clinical manifestations of malignant melanoma. These disorders can be classified as: neoplastic melanocytic disorders of choroid except for malignant melanoma, such as nevus and melanocytoma; neoplastic non-melanocytic disorders of choroid, such as leiomyoma, schwannoma, lymphoma and metastatic disorders; and non-neoplastic space-occupying lesions, such as hemorrhage, granuloma and chronic uveitis with thickening of choroid such as Vogt-Koyanagi-Harada syndrome (VKH). These lesions may be similar to melanoma in clinical manifestations, echography, and other imaging studies such as CT scan or MRI. For this reason in a patient with suspected malignant melanoma we should rule out other mimicking lesions that can be managed with conservative treatments.

Non-Hodgkin lymphoma (NHL) is one of the masquerade syndromes of malignant melanoma that occur with two main patterns of presentations in the

Received: 6 Mar. 2005, Revised: 18 Jun. 2005 , Accepted: 21 Jun. 2005

*** Corresponding Author:**
F. Asadi-Amoli, Eye Research Center, Farabi Eye Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 55414941-6
Fax: +98 21 5548080
E-mail: path1383@yahoo.com

eye. First type primarily involves lymph nodes and affects the eye by metastatic involvement of uveal tissue. The second pattern is mainly extranodal and ocular involvement primarily affects the retina (1-5). Primary intraocular lymphoma (PIOL) is a subset of NHL of central nervous system (NHL-CNS) which mainly involves the retina, and often masquerades melanoma. Latter type can arise from the brain, spinal cord, leptomeninges, or eye (6). Most commonly primary intraocular B-cell lymphomas occur in association with CNS involvement. On the other hand patients with NHL-CNS often present with ocular manifestations before development of neurologic involvement. The most common symptoms include blurred vision and floaters, and the most common findings are vitritis (66%), anterior chamber cell (43%), and cream colored-subretinal yellow infiltrates (41%) (6).

Diagnosis of NHL-CNS or PIOL is based on the identification of malignant cells in the eye by vitreous biopsy or by biopsy of other ocular tissues, such as chorioretinal biopsy (7-8). Immunohistochemistry performed on suspicious cells aids the diagnosis, because the majority of PIOLs are of B-cell lineage. The finding of B-cell markers with a kappa or lambda light chain monoclonal response confirms the diagnosis. In PIOL chorioretinal biopsy will show malignant cells between Bruch's membrane and retinal pigment epithelium (RPE). While reactive cells can be seen in the retina, their numbers are limited. In the choroid this reaction is much more significant (6, 9-11). Though PIOL cells have been identified in the retina, optic nerve, ciliary body, and iris of patients with NHL-CNS or PIOL, these sites have often been infiltrated with CNS involvement during or after diagnosis. In PIOL, choroids ordinarily can show reactional response and not primary involvement with tumor cells. We present the clinical and histopathologic findings in a patient with diffuse infiltration of PIOL cells in the choroids (primary choroidal lymphoma without systemic or CNS involvement) who has been enucleated with diagnosis of malignant melanoma.

CASE REPORT

A 37-year-old woman presented with a 4-week history of decreased vision and floaters in her right eye. Visual acuity was LP in her right eye and 10/10 in the left. She had 2+ APD in her right eye. Ocular tensions were 46 mmHg in the right and 12mmHg in the left. Slit lamp examination revealed normal anterior segment with 2+ vitritis in right eye. Fundoscopic examination of the right eye was significant for the presence of 2+ vitreous haze, 2+ vitreous cells and exudative retinal detachment. Left eye examinations were normal. B-scan echography of the right eye showed retinal detachment and choroidal thickening (Fig. 1). MRI showed semilunar shape lesion in the posterior aspect of right globe and abnormal signal intensity within the vitreous which seemed to be due to choroidal melanoma with sub-retinal exudates or hemorrhage (Fig. 2). Systemic work-up was done to show any underlying disease. Lymphadenopathy or splenomegaly was not found.

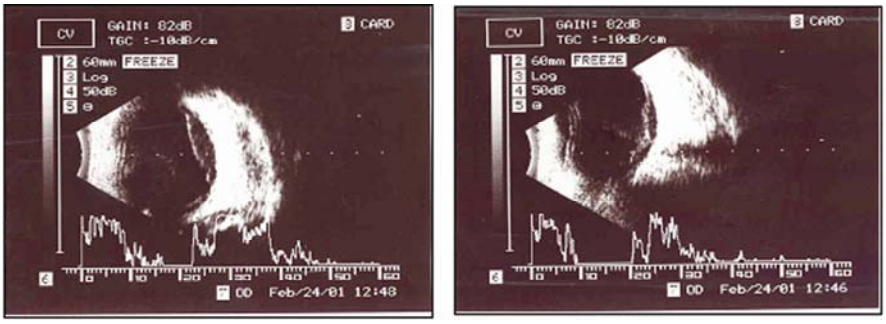
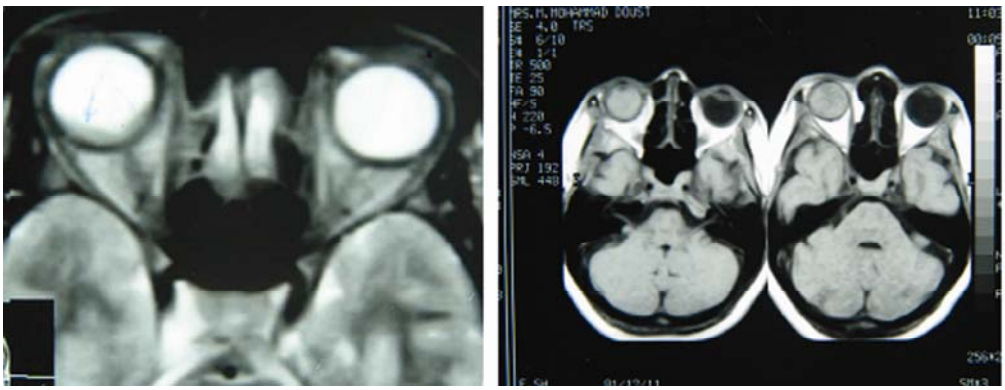


Fig. 1. Ultrasonography shows choroidal thickening and retinal detachment with internal echoes in sub-retinal fluid.



A **B**

Fig. 2. T2-weighted magnetic resonance image shows semilunar shape lesion in the posterior aspect of the right globe (A). T1-weighted magnetic resonance axial image shows abnormal intensity within the vitreous (B) was considered to be due to choroidal melanoma with sub-retinal hemorrhage or exudates.

Liver function tests and hematologic tests were normal. Brain, chest, and abdominal CT scans were reported to be normal. The patient underwent enucleation with clinical suggestion of choroidal melanoma.

Histologic report

Specimen submitted for pathologic examination (Fig. 3) consisted of an eyeball measured 2.5 cm in antero-posterior diameter which had relatively hard consistency with a whitish mass measured 3 mm in thickness in posterior two-third of choroid near the optic nerve without optic nerve involvement. In addition to this mass retinal detachment vitreous opacity can be seen grossly. Histologic examination revealed diffuse infiltration of the choroid with a tumor composed of round, uniform large cells with moderate to large nucleoli and scant cytoplasm (Fig. 4). Microscopic examination of retina showed retinal detachment with mild atrophy and gliotic changes without malignant cell infiltration. Pigment-laden macrophages could be seen sparsely in the vitreous without malignant cells infiltration. Immunohistochemistry staining showed a negative staining for HMB-45 and CD3, a positive staining for LCA, and CD20. A diagnosis of malignant NHL, diffuse large B-cell type, was confirmed (Fig. 4).

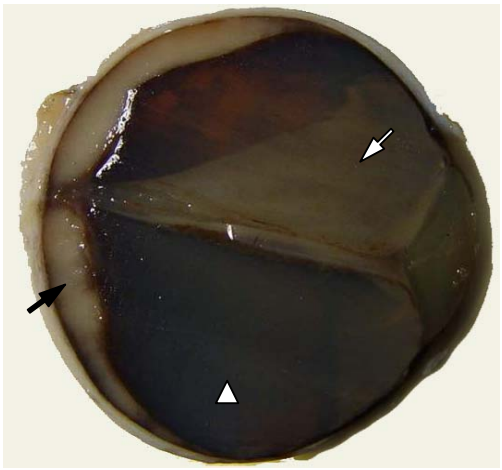
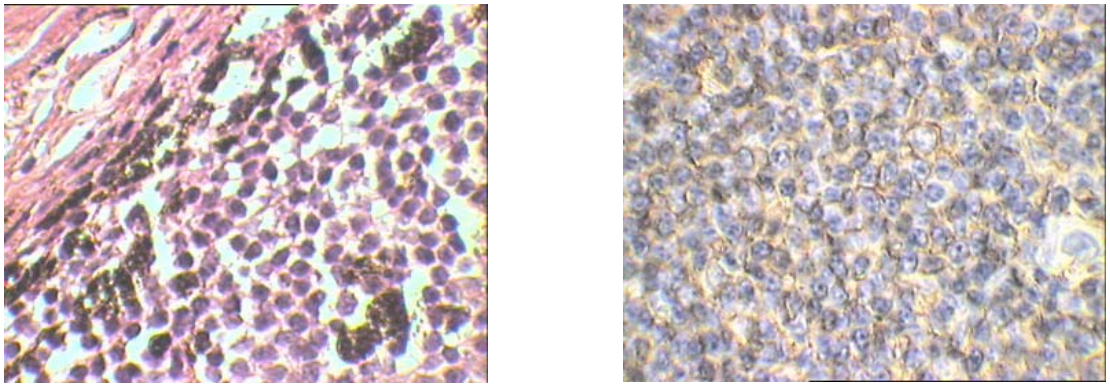


Fig. 3. Choroidal lymphoma, gross pathology. Diffuse thickening of choroid due to whitish mass in posterior two-third of choroids (black arrow), retinal detachment (white arrow), and vitreous opacity (arrow head) can be seen grossly.

After taking histologic report, the patient underwent lumbar puncture and systemic work-up for NHL, which was normal at that time. Results of other investigations including bone-marrow aspirates, body computed tomography, whole-body scan, and MRI were normal. The patient was followed by a hematologist and a neurologist. Multiple periodic lumbar puncture, bone-marrow aspirates, and imaging studies were normal. Subsequent follow-up showed no recurrence of tumor and no significant finding in systemic work-up within 36-months of follow-up.



A **B**

Fig. 4. The histological examination shows infiltration of choroid with malignant cells of diffuse large B-cell lymphoma (A, sclera and choroid, 100×, H&E). The tumor cells are CD20+ (B, 100×, immunostained).

DISCUSSION

NHL involves ocular tissues either as primary tumor or as secondary metastasis from systemic disease. Presentation of intraocular lymphoma can masquerade as malignant melanoma and put the physician in a challenging problem for diagnosis. The importance of accurate diagnosis is due to this fact that the management of NHL is medical with or without radiotherapy rather than surgery with the possibility of enucleation in most of the patients with melanoma. PIOL commonly occurs in the elderly; however, younger patients have been described, particularly those who are immunocompromised (12-13). The case presented here was both young and immunocompetent with no evidence of HIV infection. Most commonly PIOLs involve the posterior segment and the patients present with reduction of vision due to vitritis presented in 66% of patients followed by anterior chamber involvement in 43% (cells/keratoprecipitates) and /or retino-choroidal involvement in 41% (6). Most often posterior segment finding precedes anterior segment involvement. However, anterior segment involvement presenting as iridocyclitis and glaucoma can precede detection of sub-retinal infiltrates (10-11). Histopathologic examination of the anterior chamber of eyes with PIOL often demonstrates reactive and inflammatory cells. On rare occasions abnormal lymphoid cells have been retrieved from anterior chamber of some patients by fine needle aspiration (FNA) (14).

Uveal infiltration by malignant cells in large B-cell lymphoma has been already documented (15). In PIOL, however, choroidal involvement has not been reported although only a handful of patients with iris or ciliary- body involvement have been reported (6). The mechanism of uveal invasion by malignant cells remains to be a mystery. As mentioned earlier, histopathologic reports of PIOLs usually show predominantly inflammatory rather than malignant cells in the choroid.

The patient presented here seems to be the first reported case in whom primary choroidal NHL was diagnosed without involvement of retina and CNS or systemic involvement. The mean age of the patient with PIOL is between the 50^{th} and 60^{th} years with slight male predominance (7). Three populations at risk of developing NHL-CNS are patients with AIDS, transplant recipients, and patients with congenital immunodeficiency. All patients suspected of having PIOL should undergo a neurologic work-up including lumbar puncture and examination of cerebrospinal fluid, and MRI of brain. Patients with systemic lymphoma and metastasis to choroid often have other findings such as lymphadenopathy or mediastinal mass. These patients should undergo systemic work-up with bone-marrow biopsies and CT-scan of chest or abdomen (7). In our case, however, both of them were negative. On the other hand, primary site of the PIOL was choroid not retina.

In recent years FNA has been proposed both for much of the intraocular and extraocular tumors (16-

18). This method often provides enough material for histologic examination and confirmation of histologic type, and helps to choose the best approach. The positive predictive value of intraocular fluids cytology has been suggested to be 92% (16). The accuracy of FNA cytology in evaluating eyelid masses was 89.4% (18). FNA especially is important in masquerade syndromes of melanoma, such as lymphoma. In our patient if a biopsy had been done before surgery, and lymphoma rather than malignant melanoma had been suggested, she could have saved her eye.

The diagnosis of PIOL by vitreous, chorioretinal, or subretinal biopsy has been previously described (4, 5, 7, 8, and 19). Identification of lymphoma cells in the vitreous is commonly the gold standard for diagnosis of this disease (7, 19). Cells have also been identified in the aqueous (20). Retrieval of cells from intraocular fluids, however, can often be inconclusive and tissue diagnosis is often necessary, requiring an invasive chorioretinal or sub-retinal biopsy. Sometimes an iris biopsy may provide valuable information even in patients with little clinical evidence of tumor invasion (6).

In summary, although primary intraocular large B-cell lymphoma is considered mostly a disease of retina with or without CNS involvement, this article provides evidence for choroidal origin in some cases without CNS or systemic involvement. We recommend confirming histologic type of tumor by performing FNA in patients with atypical malignant melanoma. This is, to our best knowledge, the first case diagnosed as primary choroidal NHL without CNS or systemic involvement.

REFERENCES

1. Neudorfer M, Kessler A, Anteby I, Goldenberg D, Barak A. Co-existence of intraocular and orbital lymphoma. Acta Ophthalmol Scand. 2004 Dec; 82(6):754-761.
2. Siepmann K, Rohrbach JM, Duncker G, Zierhut M. [Intraocular non-Hodgkin's lymphoma and its therapy--a case series of ten patients]. Klin Monatsbl Augenheilkd. 2004 Apr; 221(4):266-272. German.
3. Weissman SS. Masquerade syndromes. Ophthalmol Clin N Am 1993; 6:127-137.
4. Char DH, Ljung BM, Miller T, Phillips T. Primary intraocular lymphoma (ocular reticulum cell sarcoma) diagnosis and management. Ophthalmology. 1988 May; 95(5):625-630.
5. Freeman LN, Schachat AP, Knox DL, Michels RG, Green WR. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology. 1987 Dec; 94(12):1631-1639.
6. Velez G, de Smet MD, Whitcup SM, Robinson M, Nussenblatt RB, Chan CC. Iris involvement in primary intraocular lymphoma: report of two cases and review of the literature. Surv Ophthalmol. 2000 May-Jun; 44(6):518-526.
7. Whitcup SM, de Smet MD, Rubin BI, Palestine AG, Martin DF, Burnier M Jr, Chan CC, Nussenblatt RB. Intraocular lymphoma. Clinical and histopathologic diagnosis. Ophthalmology. 1993 Sep; 100(9):1399-1406.
8. Blumenkranz MS, Ward T, Murphy S, Mieler W, Williams GA, Long J. Applications and limitations of vitreoretinal biopsy techniques in intraocular large cell lymphoma. Retina. 1992; 12(3 Suppl):S64-70.
9. Buggage RR, Velez G, Myers-Powell B, Shen D, Whitcup SM, Chan CC. Primary intraocular lymphoma with a low interleukin 10 to interleukin 6 ratio and heterogeneous IgH gene rearrangement. Arch Ophthalmol. 1999 Sep; 117(9):1239-1242.
10. Raju VK, Green WR. Reticulum cell sarcoma of the uvea. Ann Ophthalmol. 1982 Jun; 14(6):555-560.
11. Vogel MH, Font RL, Zimmerman LE, Levine RA. Reticulum cell sarcoma of the retina and uvea. Report of six cases and review of the literature. Am J Ophthalmol. 1968 Aug; 66(2):205-215.
12. Schanzer MC, Font RL, O'Malley RE. Primary ocular malignant lymphoma associated with the acquired immune deficiency syndrome. Ophthalmology. 1991 Jan; 98(1):88-91.
13. Rivero ME, Kuppermann BD, Wiley CA, Garcia CR, Smith MD, Dreilinger A, Freeman WR. Acquired immunodeficiency syndrome-related intraocular B-cell lymphoma. Arch Ophthalmol. 1999 May; 117(5):616-622.
14. Trudeau M, Shepherd FA, Blackstein ME, Gospodarowicz M, Fitzpatrick P, Moffatt KP. Intraocular lymphoma: report of three cases and review of the literature. Am J Clin Oncol. 1988 Apr; 11(2):126-130.

15. Duker JS, Shields JA, Ross M. Intraocular large cell lymphoma presenting as massive thickening of the uveal tract. Retina. 1987 Spring; 7(1):41-45.
16. Davila RM, Miranda MC, Smith ME. Role of cytopathology in the diagnosis of ocular malignancies. Acta Cytol. 1998 Mar-Apr; 42(2):362-366.
17. Char DH, Miller TR, Crawford JB. Cytopathologic diagnosis of benign lesions simulating choroidal melanomas. Am J Ophthalmol. 1991 Jul 15; 112(1):70-75.
18. Arora R, Rewari R, Betheria SM. Fine needle aspiration cytology of eyelid tumors. Acta Cytol. 1990 Mar-Apr; 34(2):227-232.
19. Char DH, Ljung BM, Deschenes J, Miller TR. Intraocular lymphoma: immunological and cytological analysis. Br J Ophthalmol. 1988 Dec; 72(12):905-911.
20. Sullivan SF, Dallow RI. Intraocular reticulum cell sarcoma: its dramatic response to systemic chemotherapy and its angiogenic potential. Ann Ophthalmol. 1977 Apr; 9(4):401-406.