Bilateral Idiopathic Sclerosing Inflammation of the Orbit: Report of Three Cases

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We report 3 cases of bilateral orbital sclerosing inflammation and review the literatures concerning bilateral idiopathic orbital inflammation. We found that when idiopathic orbital inflammation presents as a bilaterally diffuse retrobulbar apical mass, the sclerosing subtype must be considered first, and an orbital biopsy should be performed. The present cases were characterized by chronic-onset, cicatricial inflammation with a mass effect. The most common ocular findings in our study were vision decrease, proptosis, and restriction of extraocular muscle movement. We found that current treatment, using systemic corticosteroids and radiotherapy, was nonspecific, incomplete, or frequently resulted in relapse. For cases refractory to corticosteroids and radiotherapy, early and aggressive multiagent immunosuppressive therapy should be used to minimize visual and ocular disabilities. *(Chang Gung Med J 2004;27:758-65)*

Key words: idiopathic orbital inflammation, idiopathic orbital sclerosing inflammation.

Idiopathic sclerosing inflammation of the orbit is a distinct clinicopathologic entity characterized by slow and relentless involvement of orbital structures as opposed to more-typical acute or subacute presentations of other forms of idiopathic orbital inflammation.[1] Histologically, the amount of interstitial connective tissue is disproportionately great, and the inflammatory infiltrate is paucicellular. In the past, idiopathic sclerosing inflammation was presumed to be an end-stage lesion following chronic, recurrent, or severe inflammation in the orbit, in which the lymphocytic inflammation present in the acute and subacute phase was replaced by fibroplasias in the chronic or sclerosing phase. However, recent evidences pointed out that a cell-mediated immunopathologic mechanism may be responsible for this desmoplastic finding. Typically, idiopathic orbital inflammatory syndrome presents with a unilateral, acute clinical course. Bilateral presentation is rare in adults, and a chronic, insidious course makes distinction from neoplastic lesions clinically difficult. Therefore, we report 3 cases of bilateral idiopathic orbital inflammation, which were proven by biopsy to be sclerosing inflammation. We also review 7 previously reported cases of manifesting bilateral idiopathic orbital inflammation to evaluate their clinical and histopathologic features.

CASE REPORTS

Case 1

A 36-year-old man presented in February 1985 with the complaint of bilateral vision disturbance for about 6 months. At that time, the right and left visual acuity (VA) were 20/50 and 20/400, respectively. Marked proptosis and restricted extraocular muscle

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movement were found. Computed tomography (CT) showed a bilateral orbital homogenous apical mass (Fig. 1A). The disease process was relentlessly progressive despite treatment with systemic steroids and radiotherapy (5400 cGy). The orbital mass increased in size, proptosis worsened, and vision declined (OS > OD) in the following 6 months. Therefore, bilateral orbital tumor excision through a bifrontal craniotomy was arranged by the neurosurgeon. This only resulted in temporary visual improvement. The pathologic report from this procedure showed an idiopathic sclerosing inflammation (Fig. 2). In the next 5 years, the bilateral orbits were occupied by a diffuse "fibrotic" mass (Fig. 1B), and his vision deteriorated to counting finger at 30 cm in the right eye and no light perception in the left eye. During this period, we tried to improve his vision and resolve the proptosis by performing right orbital decompression. However, the ability of sclerotic tissues to expand is limited, and no significant clinical effect was observed.

Case 2

A 59-year-old female was sent to our hospital emergency room with sudden onset of proptosis, ophthalmoplegia, and vision deterioration in both eyes. At that time her vision was 20/50 in the right eye and 20/60 in the left eye. The CT scan of the orbit showed a diffuse retrobulbar mass in both orbits. There was no contiguous sinus or intracranial disease. Then the patient underwent a medial orbitotomy, and the biopsy revealed dense collagenous stroma with a lymphoplasmacytic inflammatory infiltrate consistent with idiopathic sclerosing orbital inflammation. Initially, the patient was treated with

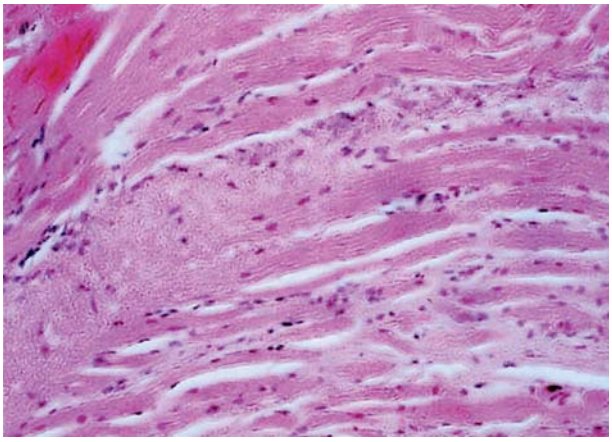

Fig. 2 Case 1. Biopsy specimen shows a sparse inflammatory cell infiltrate within streaming bands of dense collagenous stromata. Muscle fibers are swollen and separated by edema and fibrosis. (hematoxylin & eosin, ×400)

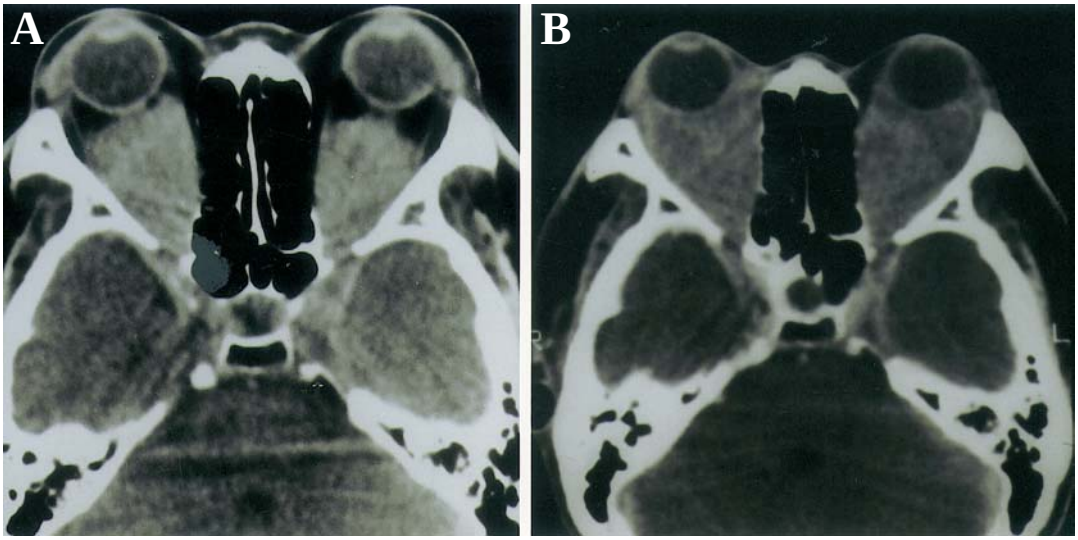

Fig. 1 (A) Case 1. Initial computed tomographic scan of the orbits shows the bilateral orbital apical mass. (B) Follow-up computed tomographic scan showing progression of the infiltrative mass to involve the entire orbits, despite systemic steroids, radiotherapy, and orbital decompression treatment.

high-dose systemic steroids but without improvement. Radiotherapy with 4250 cGy was arranged later. Her vision improved to 20/30 in the right eye and 20/50 in the left eye. However, long-term follow-up could not be obtained, because the patient expired due to a multiple cerebral infarction 3 months later.

Case 3

A 74-year-old male presented in February 2001 with a 2-year history of red eyes, proptosis, and reduced vision. Additional findings on ocular examination included limitation of ocular movement, a left relative afferent papillary defect, bilateral pale optic discs, and macular edema. The right and left VA were 20/300 and CF/60 cm at the initial examination. A diffuse mass without a distinct margin extending from the orbital apex into the anterior eyelid surface was found on MRI scan (Fig. 3A). A subsequent biopsy of the lesion from the left orbitotomy showed a dense collagenous stroma with lymphoplasmacytic inflammatory infiltrate extending into the orbital fat consistent with idiopathic sclerosing orbital inflammation. Systemic evaluations including thyroid function, abdominal CT, and antinuclear cytoplasmic antibody were negative.

After a course of intravenous steroids with subsequent slowly tapered oral steroids over a 2-month period, his visual acuity improved to 20/100 in the right eye and 20/1000 in the left eye. The proptosis markedly decreased, and ocular motility returned to normal. A CT scan after the systemic steroids showed that the orbital mass had been reduced in size by nearly 30% (Fig. 3B).

However, recurrent proptosis and visual deterioration of the right eye were noted in the following 2 years. Although he continued to receive systemic steroids, the vision in his right eye continued to deteriorate. Then, the patient received radiotherapy (2000 cGy) to control the disease progression.

A review of the literature[1-6] identified 7 patients who presented with bilateral idiopathic orbital inflammation. Table 1 shows the characteristics regarding clinical features, radiologic findings, histopathologic analyses, therapies, outcomes, and associated systemic diseases. Although detailed information was not provided in all of these studies, the following characteristics were found (including our 3 cases):

1. The mean age was 51 (range, 36 to 74) years;
2. The gender reported for 9 patients was 6 males and 3 females;
3. The disease affected both eyes simultane-

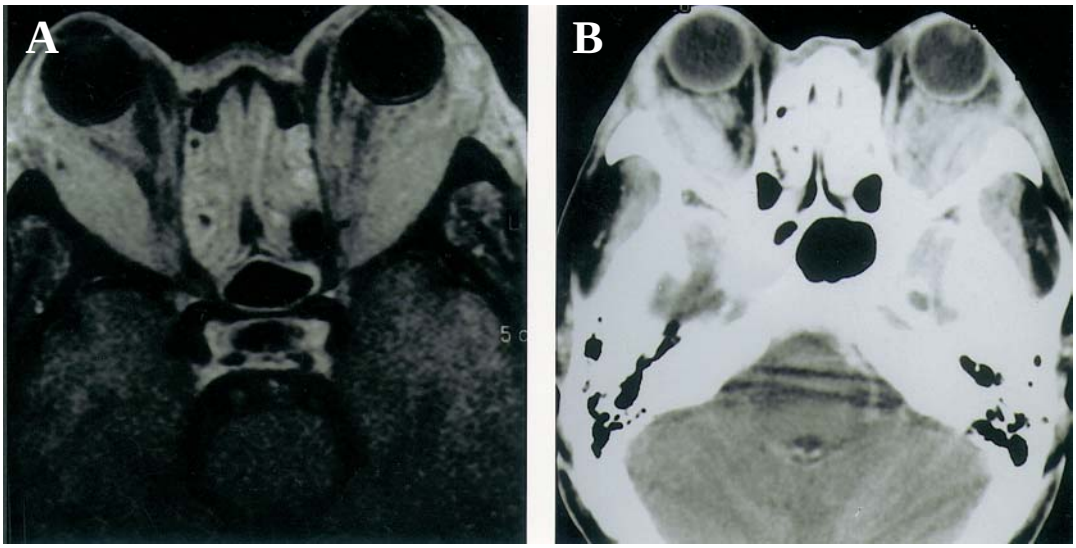

Fig. 3 (A) Case 3. Magnetic resonance imaging of the orbits demonstrates an infiltrative retrobulbar mass encompassing the lateral rectus muscle and extending from the orbital apex to anterior eyelid surface. (B) Computed tomographic scan after systemic steroids showing partial shrinkage of the infiltrative mass.

Table 1. Clinical Features, Radiologic Findings, Histopathologic Analyses, Therapies, Visual Outcomes, and Associated Systemic Diseases with Bilateral Nonspecific Orbital Inflammation

Study	Onset	Symptoms	Orbital image	Pathology	Management	Initial VA OD OS	Final VA OD OS	Systemic Disease
Colley 1935[2]	Chronic	Proptosis, ophthalmoplegia, VA decrease	Diffuse mass extending anteriorly to posteriorly	Suggested sclerosing inflammation	NA	OD: 6/9 OS: NS	OD: NLP OS: NS	NA
Schonder et al. 1985[3]	Acute, alternating	Eye pain (+anterior uveitis), proptosis, ophthalmoplegia	Diffuse infiltration with slight bony erosion	Lymphoid inflammation, fibrotic tissue (-)	Systemic steroids, NSAIDs	OU: 20/25	OU: 20/20	Retroperitoneal fibrosis
Frohman et al. 1986[4]	Chronic	Proptosis, ophthalmoplegia, VA decrease	Extensive diffuse mass and bony destruction	Idiopathic sclerosing inflammation	Previous orbital decompression, systemic steroids, R/T	OU: NS	OU: NLP	
Levine et al. 1993[5]	Chronic	Visual decrease, mild adduction limitation	Diffuse retrobulbar mass	Idiopathic sclerosing inflammation	Systemic steroids, R/T, azathioprine	OD: 20/25 OS: 20/40	OD: 20/25 OS: 20/60	Retroperitoneal fibrosis
Rootman et al. 1994[1]	Chronic	Eye pain, diplopia	Apical mass	Idiopathic sclerosing inflammation	Observation	OD: 20/20 OS: 20/15	OU: 20/20	
Rootman et al. 1994[1]	Chronic	Eye pain, VA decrease	Lacrimal gland enlargement	Idiopathic sclerosing inflammation	Systemic steroids, R/T, NSAIDs, cyclophos-phamide	OD: 20/20 OS: 20/15	OU: 20/20	
Lai et al. 2000[6]	Acute	Eye pain, blurred vision, proptosis	OD: soft tissue mass over the LRM and superolateral aspect OS: apex mass	Chronic inflammation	Systemic steroids, azathioprine	OD: 20/200 OS: 20/25	OU 20/20	Suprasellar and pulmonary pseudotumor
Our present cases	Chronic	Proptosis, ophthalmoplegia, VA decrease	Apical mass with intracranial extension	Idiopathic sclerosing inflammation	Systemic steroids, R/T, surgery	OD: 20/50 OS: 20/400	OD: CF/30cm OS: NLP	
	Acute	Eye pain, proptosis, ophthalmoplegia, VA decrease	Diffuse retrobulbar mass	Idiopathic sclerosing inflammation	Systemic steroids, R/T	OD: 20/50 OS: 20/60	OD: 20/30 OS: 20/50	
	Chronic	Proptosis, ophthalmoplegia, VA decrease	Diffuse retrobulbar mass from apex to anterior eyelid	Idiopathic sclerosing inflammation	Systemic steroids, R/T	OD: 20/300 OS: CF/60cm	OD: 20/100 OS: 20/1000	

Abbreviations: OD: right eye; OS: left eye; R/T: radiotherapy; NA: not applicable; NS: not specified; NLP: no light perception.

ously in 9 patients, and alternatively in 1 patient;
4. Onset was chronic (duration > 4 weeks) in 7 patients and acute (duration < 1 week) in 3 patients;
5. According to the description of signs and symptoms in the literatures, visual decrease was the most common symptom;
6. Images or detailed reports of radiologic examinations were available in 8 patients, and 5 of them had a diffuse retrobulbar mass with an irregular margin;
7. The histopathologic findings of 8 patients were compatible with a diagnosis of idiopathic orbital sclerosing inflammation;
8. Of the patients treated with systemic steroids (8 cases), 7 had an initial response, but 5 cases were reported to recurrent later.
9. Of the patients (6 cases) treated with radiotherapy, 5 responded, with 3 experiencing recurrence;
10. Three patients received chemotherapy combined with systemic steroids to achieve a stable effect;
11. Three patients had a coexisting systemic disease.

DISCUSSION

Idiopathic orbital inflammation is not an uncommon lesion in adults, accounting for 13% of cases of unilateral exophthalmos, ranking second only to Grave's disease as a cause for this condition. The exact pathogenesis of idiopathic orbital inflammation is unclear, but the available evidence suggests an autoimmune response directed against various target tissues in the orbit. Therefore, the inflammatory process can be divided into myositis, lacrimal, anterior, apical, and diffuse on the basis of differences in presentation and clinical findings. Among these locations, orbital myositis is thought to have a higher percentage of occurring bilaterally. Some studies showed bilaterality to occur in 0% to 11%,[7,8] whereas other studies with longer follow-up found bilaterality of approximately 50%.[9] Meanwhile, bilateral manifestations appear to be more common in the pediatric population.[10,11] Such idiopathic orbital inflammation presenting as a bilateral diffuse retrobulbar mass in an adult, as in our 3 cases, is rare. Their biopsies were consistent with idiopathic sclerosing orbital inflammation. We also reviewed 7 previously reported cases of bilateral idiopathic orbital inflammation, and the histologic findings of 5 cases were sclerosing inflammation. In our previous report on sclerosing orbital inflammation, 2 of 6 patients presented bilaterally.[12] Because of our limited cases, we cannot establish that idiopathic orbital sclerosing inflammation has a higher percentage to present bilaterally. However, idiopathic orbital inflammation with bilateral orbit involvement, especially the diffused type, has a high tendency to be expressed as the sclerosing type.

Because nonspecific orbital inflammations are predominately unilateral, their diagnosis must exclude any other possible etiology. Therefore, the possibility of local and systemic inflammatory processes such as thyroid orbitopathy, sarcoidosis, Wegener's granulomatosis, orbital lymphoid tumors, and secondary metastasis from breast, bowel, or prostatic carcinomas should be considered. Sarcoidosis and Wegener's granulomatosis show bilateral involvement in 75% and 85% of cases, respectively.[15,14] However, orbital sarcoidosis is found in lacrimal glands approximately 90% of the time.[13] In active orbital sarcoidosis, serum ACE levels are elevated. Wegener's granulomatosis often shows ear, nose, throat, and chest symptoms on examination. The CT feature suggestive of Wegener's granulomatosis is involvement of sinus structures. In addition, c-ANCA testing can be used for early diagnosis. Bilateral orbital involvement in females may be considered a possibility of metastatic breast carcinoma. Of 180 reported cases of orbital breast metastases, 36 (20%) were noted to be bilateral on initial presentation and follow-up evaluation.[15-17] However, between 74% and 89% of patients present with a known history of primary breast carcinoma, and the majority of patients have concomitant nonorbital metastasis at the time of presentation.[16] In a study by McNally et al.,[18] 9 of 100 patients (9%) were discovered to have a bilateral orbital lymphoid tumor. So bilateral orbital lesions are an absolute indication for orbital biopsy. Even if one highly suspects the bilateral lesions to be due to idiopathic orbital inflammation based on clinical or radiologic presentations and the steroid response, these cannot be used as the criteria for a correct diagnosis. If the diagnosis is wrong or late, the visual or systemic consequences

can be great.

Among our patients and the previously reported cases, over 60% presented with a retrobulbar apical mass. With a tendency of posterior and perioptic nerve infiltration, a visual decrease was the early complaint. In this study, we found that bilateral idiopathic orbital inflammation tends to have a chronic onset (over 4 weeks) and is characterized by signs of indolent inflammation and a mass effect. Vision disability, proptosis, and restriction of extraocular muscle movement were the most common ocular findings. Pain was reported to be less severe. Treatment of idiopathic orbital inflammation primary is based on immunosuppression with systemic corticosteroids as the first choice. However, as observed in our patients, although they did have initial responses to steroid therapy, incomplete resolution or rebound of symptoms after the steroids taper was found. Radiation therapy is an alternative for patients who are unresponsive to steroids, who become steroid-dependent, or who have intolerable adverse reactions to steroids.[19] But some recurrences (3 of 6 patients) were found in our study, so long-term observation is needed. Surgical resection may be effective for more-localized lesions.[20] However, it is difficult and dangerous for diffused, posterior orbital tumors because of the involvement of vital structures. We tried orbital decompression in 1 patient (case 1), and results demonstrated that creating a larger orbital space is ineffective in releasing the sclerosing lesion. Immunosuppressive chemotherapy such as cyclophosphamide or azathioprine therapy in combination with systemic corticosteroids was found to be effective in 3 patients from the reviewed articles.[1,5,6] Rootman et al. emphasized that the lack of a specific therapy and delay of an effective therapy for idiopathic orbital sclerosing inflammation are largely responsible for poor outcomes and advised clinicians to pursue early and aggressive multiagent immunosuppressive therapy.[1] However, reports of chemotherapy are fairly limited in idiopathic orbital inflammation, and standard therapeutic protocols are currently lacking, so we selected a conservative manner for chemotherapy in our 3 cases.

In conclusion, we report 3 cases of bilateral orbital sclerosing inflammation and review the literatures concerning bilateral idiopathic orbital inflammation. We found that when idiopathic orbital inflammation presents as a bilateral, diffuse retrobulbar apical mass, the sclerosing subtype must be considered first. Then an orbital biopsy should be performed to confirm the histopathologic evidence. For diffused retrobulbar lesions, when apparent fibrosis is established, treatment is difficult and often unsuccessful. The current strategy of systemic corticosteroids and radiotherapy is nonspecific and incomplete and frequently results in recurrence. Alternatively, early and aggressive multiagent immunosuppressive therapy may be used to minimize visual and ocular disabilities.

REFERENCES

1. Rootman J, McCarthy M, White V, Harris G, Kennerdell J. Idiopathic Sclerosing Inflammation of the Orbit. Ophthalmology 1994;101:570-84.
2. Colley T. A case of inflammatory pseudo-tumor of the orbit. Br J Ophthalmol 1935;19:93-5.
3. Schonder AA, Clift RC, Brophy JW, Dane LW. Bilateral recurrent orbital inflammation associated with retroperitoneal fibrosclerosis. Br J Ophthalmol 1985;69:783-7.
4. Frohman LP, Kupersmith MJ, Lang J, Reede D, Bergeron RT, Aleksic S, Trasi S. Intracranial extension and bone destruction in orbital pseudotumor. Arch Ophthalmol 1986;104:380-4.
5. Levine MR, Kaye L, Mair S, Bates J. Multifocal fibrosclerosis. Arch Ophthalmol 1993;111:841-3.
6. Lai YH, Wang HZ, Tsai RK, Hoyt WF, Lee BF. Bilateral orbital pseudotumor with suprasellar and pulmonary involvement. J Neuro-Ophthalmology 2000;20:268-72.
7. Siatkowski RM, Cap'o H, Byrne SF, Gendron, EK, Flynn JT, Munoz M, Feuer WJ. Clinical and echographic finding in idiopathic orbital myositis. Am J Ophthalmol 1994; 118:343-50.
8. Moorman CM, Elston JS. Acute orbital myositis. Eye 1995;9:96-101.
9. Mombaaers I, Koornneef L. Current status in the treatment of orbital myositis. Ophthalmology 1997;104:402-8.
10. Mottow LS, Jakobiec FA. Idiopathic inflammatory orbital pseudotumor in childhood, I: clinical characteristics. Arch Ophthalmol. 1978;96:1410-7.
11. Mottow LS, Jakobiec FA, Smith M. Idiopathic inflammatory orbital pseudotumor in childhood, II: results of diagnosis tests and biopsies. Ophthalmology. 1981;88:565-74.
12. Wu SC, Chuang HC, Kao LY, Ma L, Ching Y. Sclerosing nonspecific orbital inflammatory syndrome. Transaction of Ophthalmological Society of Republic of China. 1992; 31:317-24.
13. Mombaerts I, Schlingemann RO, Goldschmeding R, Koornneef, L. Idiopathic granulomatosis orbital inflammation. Ophthalmology 1996;103:2135-41.
14. Perry SR, Rootman J, White VA. The clinical and pathologic constellation of Wegener granulomatosis of the

orbit. Ophthalmology 1997;104:683-94.
15. Toller KK, Gigantelli JW, Spalding MJ. Bilateral orbital metastases from breast carcinoma. Ophthalmology 1998; 105:1897-901.
16. Goldberg RA, Rootman J, Cline RA. Tumors metastatic to the orbit: a changing picture. Surv Ophthalmol 1990; 35:1-24.
17. Goldberg RA, Rootman J. Clinical characteristics of metastatic orbital tumors. Ophthalmology. 1990;97:620-4.
18. McNally L, Jakobiec FA, Knowles DM. Clinical, morphologic, immunophenotypic and molecular genetic analysis of bilateral ocular adnexal lymphoid neoplasms in 17 patients. Am. J. Ophthalmol1987;103:555-68
19. Lanciano R, Fowble B, Sergott RC. The results of radiotherapy for orbital pseudotumor. Int J Radiat Oncol Biol Phys 1990;18:407-11
20. Char DH, Miller T. Orbital pseudotumor: fine-needle aspiration biopsy and response to therapy. Ophthalmology. 1993;100:1702-10.

兩側眼框非特異性炎症

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我們在此呈現了3個兩側同時表現眼框非特異性炎症 (idiopathic orbital inflammation) 的病人，而他們的病理切片證實爲特殊的硬化性發炎 (idiopathic orbital sclerosing inflammation)。我們也從以前的文獻資料探討相關實例。

發現如果病人以兩側眼框後尖部且界限不明之浸潤性腫塊來表現眼眶非特異性炎症時，那就要高度懷疑是屬於硬化型這種特殊的組織病理變化且建議作病理切片確定。因爲這種非特異性眼眶硬化型發炎通常爲較差的預後。這些病人臨床上大多以慢性發病，而視力減退、突眼及眼球運動受阻爲最常見的眼科表現，同時他們對於類固醇或放射線治療有時並不令人滿意。所以對於這些治療效果不佳者，我們建議早期且積極的給予多種免疫性抑制性藥物治療。(長庚醫誌 2004;27:758-65)

關鍵字：眼框非特異性炎症，非特異性眼眶硬化型發炎。

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