# PARANEOPLASTIC OPTIC NEUROPATHY IN NASOPHARYNGEAL CARCINOMA - REPORT OF A CASE

S T Hoh, M Teh, S J Chew

*ABSTRACT*

***A 31-year-old Chinese man developed left optic neuritis with left sectorial field loss as a remote effect of nasopharyngeal carcinoma. The field defect showed interesting fluctuations in response to the dosage of systemic steroid therapy. Neuropathologic findings from an exploratory craniotomy did not show any gross tumour mass around the left optic nerve nor any histological evidence of tumour infiltration. This case illustrates that "optic neuritis" could be a paraneoplastic effect of nasopharyngeal carcinoma.***

*Keywords: paraneoplastic optic neuropathy, optic neuritis, nasopharyngeal carcinoma.*

**SINGAPORE MED J 1991; Vol 32: 170-173**

## INTRODUCTION

Paraneoplastic syndromes are disorders resulting from "remote effects" of cancer and are usually defined by their clinical and pathologic features and lack of direct damage by the cancer cells on the affected organ or tissue, ie. metastasis must be excluded before a paraneoplastic syndrome can be diagnosed. Visual loss as an entity under this disorder has been reported but more as a result of photoreceptor degeneration[1-3]. Visual loss as a result of optic nerve disease is usually attributed to either infiltration or microspic cuffing of the optic nerve by cancer cells.

We report this as a case of paraneoplastic optic neuropathy associated with nasopharyngeal carcinoma.

## CASE REPORT

A 31-year-old Chinese man noticed gradual dimming and blurring of his left vision in April 1988. He was subsequently diagnosed in July 1988 as having retrobulbar neuritis. He was treated with ACTH 10 units/day for 1 week x 3 courses. After each course, there had been improvement, but a relapse occurred after only 3 days of stopping treatment.

Magnetic resonance imaging of the brain performed in August 1988 was reported to be normal. The cerebrospinal fluid contained no white blood cells and normal amounts of glucose, chlorides and proteins. CSF protein and immunoglobulin electrophoresis were normal. He was given more ACTH injections for 15 days. Dosages given were as follows: 80 units/day for 6 days, 40 units/day for 3 days, 20 units/day for 3 days and 10 units/day for 3 days. His vision again improved with treatment but worsened as soon as treatment was tailed off.

In October, he complained of left sectorial field loss and occasional ocular/retrobulbar discomfort which was not aggravated by eye movement. There were no systemic complaints and his general health was excellent. His best corrected visual acuity was Snellen 6/6 and N5 in both eyes. The intra-ocular pressure was 11 mmhg in both eyes. On examination, the discs appeared normal with a mild pallor of the left disc. There was a left relative afferent pupillary reflex. Automated threshold perimetry demonstrated a left inferior arcuate defect. He was started on T. prednisolone 30 mg/day tailing off to 10 mg on alternate days in early January 1989 (Fig 1). A local steroid injection (retrobulbar methylprednisolone 40 mg in 1 ml) was given, following which his fields improved slightly.

Magnetic resonance imaging of the brain (Fig 2) was performed on two occasions. The first scan (July 1988) was initially reported to be normal and the second scan (January 1989) demonstrated a small focus of "hyperluscence" near the left orbital apex with a mild extension along the optic nerve. On closer examination of the first scan, an almost similar lesion was seen. No gross tumour could be found. However, the scans were inadequate to conclude if definite pathology was present. A complete physical examination including nasopharyngoscopy revealed no evidence of any systemic disease or obvious lesion in the post-nasal space which may have given rise to or associated with the optic neuropathy. A working diagnosis of lymphoma or tumour infiltrate of the orbital apex was made and an exploratory craniotomy was planned.

He was given more prednisolone 10 mg/day x 1 week (Fig 1), after which, treatment was to be increased to 20 mg/day but he stopped his medication on his own for about a month. During this time his vision deteriorated. The scotoma recurred and was no longer confined to the infero-temporal field but took on an almost complete temporal hemianopia. There were no defects in his right visual field during this entire period. Systemic steroids were increased again to 25 mg/day and the scotoma improved significantly.

In March 1989, exploratory craniotomy and biopsy was performed. Grossly, no tumour mass was seen. Optic canal decompression was also carried out. Immediately post-operative, an absolute inferior altitudinal defect was noted. His fundal examination showed a left optic disc which was slightly pale compared with the right, and was more marked at the supero-temporal neuro-retinal rim corresponding to the infero-nasal field defect.

Over the subsequent weeks (Fig 1), prednisolone 60 mg/day x 2 weeks (reduced by 10 mg/week thereafter) was reinstituted. This again led to an improvement in the infero-temporal field although the nasal step defect remained

**Department of Ophthalmology**
**National University Hospital**
**Lower Kent Ridge**
**Singapore 0511**

S T Hoh
Medical Student

S J Chew, FRCSEd, FCOphth
Senior Registrar

**Department of Pathology**
**National University Hospital**

M Teh, MD, MRCPath
Senior Registrar

**Correspondence to:** Dr S J Chew

**Fig 1 - Graph showing close correlation between the dosages of systemic steroid therapy and changes in the patient's visual field. The visual defect, as recorded by Automated threshold perimetry, improved with high-dose steroid therapy but worsened as soon as dosages were stepped down. (Mean deviation is the mean elevation or depression of the patient's overall field compared to the normal, age-corrected reference. Pattern standard deviation is a measurement of the degree to which the shape of the patient's measured field departs from the normal, age-corrected reference field).**

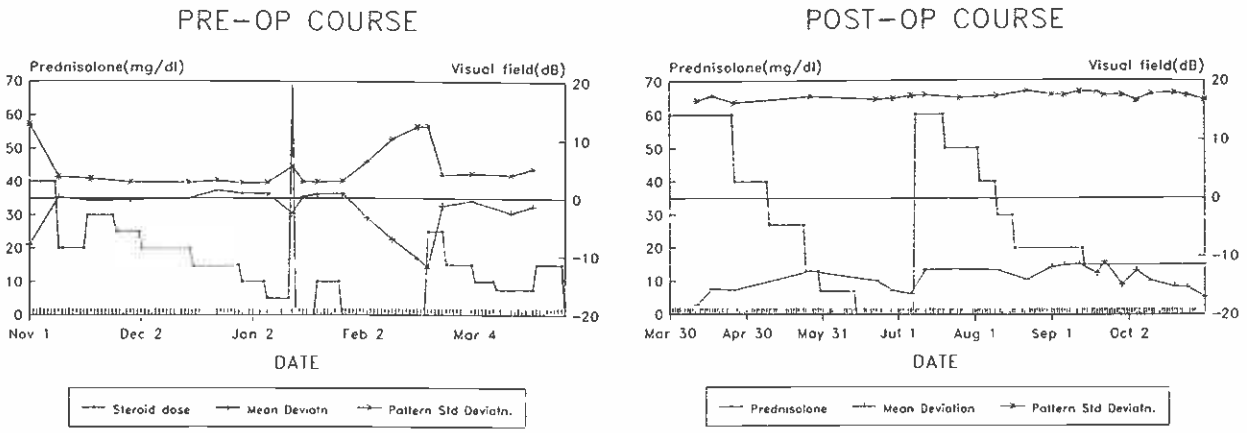
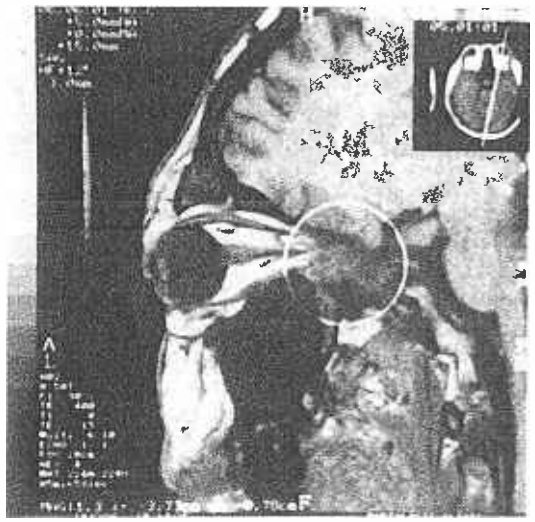
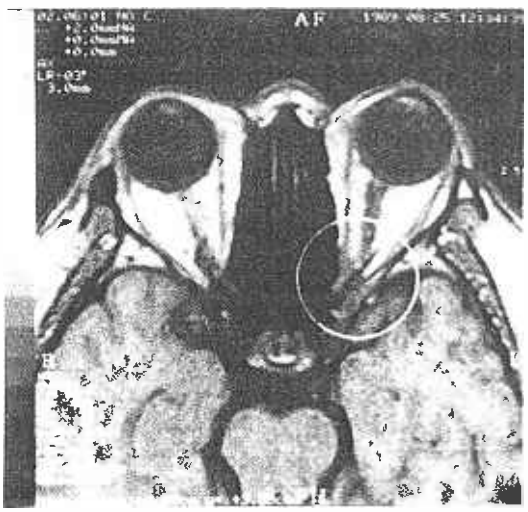



**Fig 2 - MRI demonstrating a small focus of "hyperlucence" around the optic nerve (circled). Exploratory craniotomy did not yield any abnormal findings.**





unaffected. When he was on a daily dose of 20 mg/day, an arcuate defect was again manifested. In September, the patient's steroid regime was decreased to 15 mg/day and his visual fields worsened. His blind spot has expanded and was linked to the left inferior nasal scotoma. He was reviewed weekly and initially his field was constant at 15 mg/day but in early November, his fields were noticed to be marginally worse.

In late October 1989, he presented with blood-stained saliva. EBV IgA serology was done and Anti-EBV-VCA/IgA was positive with a titre of 1:10 and Anti-EBV-Ea/IgA was negative with a titre of less than 1:5. Following this, a post-nasal biopsy was taken and based on the histopathological findings a diagnosis of nasopharyngeal carcinoma (undifferentiated type) was made. There was no obvious lymphadenopathy in the neck region. Computed tomography (Fig 3) showed an early growth at the post-nasal space with thickening of both walls more marked on the left, with no extension to the para-pharyngeal space or into the base of the skull (T1 N0 M0 - stage I).

In November 1989, at the time of writing, he was started on radical radiotherapy. His prednisolone treatment was also stepped down to 15 mg/day as it was hoped that the radiation

**Fig 3 - CT Scan showing thickening of the walls of the nasopharynx. There was also obliteration of the left eustachian tube opening (arrow).**

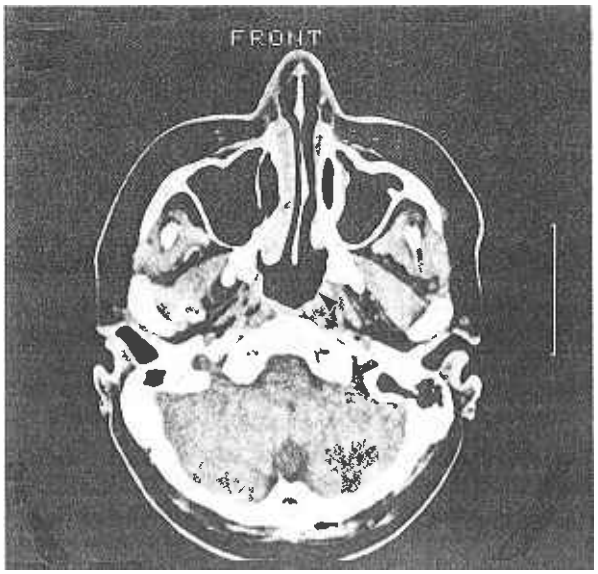


Fig 4 - (A) High power view of nasopharyngeal biopsy showing cords and small clusters of undifferentiated carcinoma cells. These are obscured by the heavy lymphoid background. (B) Peroxidase-antiperoxidase staining for a widee spectrum keratin confirms the epithelial nature of the undifferentiated cells. (Original magnification, x 500)

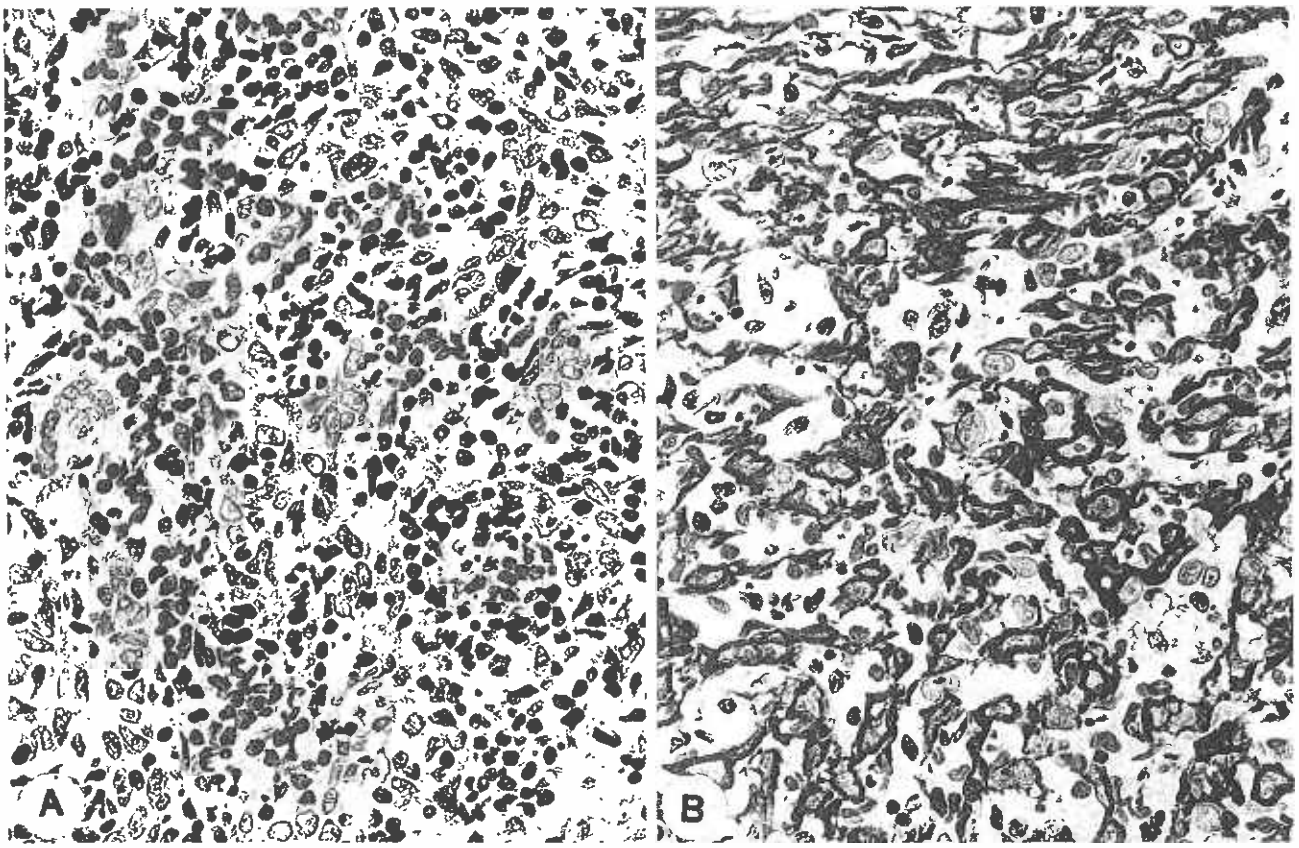
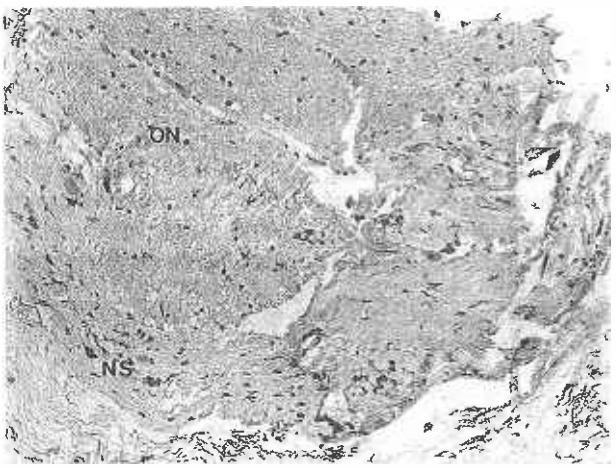



Fig 5 - Optic nerve (ON) biopsy with surrounding nerve sheath (NS) showing no evidence of tumour infiltration. (Original magnification, x 200)




would also destroy any inflammatory tissue around the optic nerve.

## PATHOLOGIC FINDINGS

Biopsies were taken from both the right and left walls of the nasopharynx (Fig 4). Both showed similar appearance and consisted of cords and small clusters of undifferentiated carcinoma cells intimately admixed with the lymphoid stroma. These cells have rounded to spindled vesicular nuclei with central nucleoli and indistinct cell boundaries. Immunoperoxidase stains for a wide spectrum of keratin (DAKO Rabbit Polyclonal Anti-keratin) were strongly positive for the carcinoma cells and showed up the cell clusters as well as the individual caricinoma cells that were obscured by the lymphoid stromal cells. Features were that of an undifferentiated nasopharyngeal carcinoma.

The optic nerve biopsy (Fig 5) consisted mainly of a small fragment of optic nerve in close apposition to the optic nerve sheath. There was no histological evidence of tumour infiltration.

## DISCUSSION

The pathological findings were early nasopharyngeal carcinoma (undifferentiated type) with no tumour infiltration or metastasis to the left optic nerve. Clinically, there was left visual loss consistent with that of optic neuropathy.

There had been several cases where paraneoplastic optic neuropathy was suggested. Richter and Moore[4] described a 43-year-old man with systemic lymphoma who developed an acute sensorimotor neuropathy associated with vision loss in the right eye and swelling of the right optic disc. Lindenberg et al[5] described a woman who experienced rapid loss of vision in the right eye in association with recurrent breast carcinoma. Pillay et al[6] described a 56-year-old man who developed bilateral internuclear ophthalmoplegia and optic neuritis in association with bronchial carcinoma. Fundal examination initially revealed a swollen left disc which later became normal whereas visual acuity deteriorated. A case reported by Boghen et al[7] was also rather similar to the one described by Pillay et al[6]. In this case a 63-year-old man developed bilateral paresis of horizontal and upward eye movements and was found to have a small oat cell carcinoma of the lung. Four months later, he experienced sudden painless visual blurring of the right eye and there was

swelling of the right eye optic disc. Three weeks later, visual acuity of the right eye improved spontaneously without any treatment. The visual field also improved and there was a decrease in the optic disc swelling.

The pathologic feature described in all these cases was a demyelination of the optic nerve in the setting of a carcinoma or lymphoma without evidence of metastasis to the central nervous system nor the optic nerve.

Unlike previous reports, we did not have full post-mortem examination. However, we believe that the same diagnosis applies to our case as we have taken several steps to prove the presence of optic neuritis without a direct infiltration or even microscopic cuffing of the optic nerve by tumour cell:

1. The onset of visual symptoms occurred before the primary lesion was found even though a deliberate search was made whereby nasopharyngoscopy done nine months after the onset showed no grossly visible lesion in the post-nasal space. Although an occult lesion could have been present at that time, such an early carcinoma is less likely to have any metastasis to the optic nerve.
2. A craniotomy, primarily exploratory in nature was carried out and grossly, no tumour mass was seen around the left optic nerve. Biopsy of the optic nerve sheath yielded no histological evidence of tumour infiltration.
3. Computed tomography showed no direct extension of the primary lesion into the base of the skull. It merely showed thickening of the nasopharyngeal walls which suggested that it was an early carcinoma (T1 N0 M0 - stage 1). Repeated MR scanning also excluded the presence of direct infiltration from the carcinoma.

We have also excluded other causes of optic neuropathy or mimickers of optic neuritis. Ischaemic optic neuropathy commonly occur in patients above 50 years with history of multiple risks factors for cerebrovascular disease. These cases usually follow a non-progressive clinical course. A compressive lesion would have been detected radiologically. Nevertheless, surgical decompression of the optic canal carried out during the craniotomy did not improve his vision. Leber's hereditary optic atrophy occurs typically in young males in their second or third decade and, the disease usually becomes bilateral within days to months and mostly by one year. Infective causes such as meningitis have been ruled out by the various blood and CSF investigations.

Although there had been several reported cases of paraneoplastic optic neuropathy (PON), none had been associated with nasopharyngeal carcinoma (NPC). As such, we report this as the first case of pathologically proven PON involving NPC.

In both the cases reported by Boghen et al[7] and Pillay et al[6], the patients were found to have disc oedema, resembling papillitis. Our patients had normal disc. Hence, retrobulbar neuritis, more common seen in adults, as opposed to papillitis, a condition generally encountered in children, was present in this case. Paradoxically, the two patients were much older (63 years and 56 years) compared with our patient.

An interesting and significant point to note was the rapid improvement in vision each time our patient was given a high-dose steroid therapy (Refer Fig 1). Even after the operation, when our patient developed an inferior altitudinal defect, probably as a result of vascular decompensation, the infero-temporal field defect continued to show fluctuations in response to treatment whereas the infero-nasal field defect remained unchanged. Boghen et al[7] reported that their patient showed spontaneous improvement in the visual acuity and fields three weeks after the onset of visual loss. Pillay et al[6] did not report any improvement of vision in their patient who died nine months after the onset. Although there are evidence suggesting that "the process can burn out leaving patients with varying degrees of disability and perhaps none at all"[8], we believe that steroids may reverse the process albeit not completely or even delay its progression. If the quality of life can be improved barring the side effects of long term treatment, steroid therapy should seriously be considered as a mode of treatment in a case of PON.

There have been an increase in recent years in the number of reports of patients with cancer who have antibodies reacting with the central nervous system[9-12]. In one study[3], a 60-year old woman presented with unexplained bilateral loss of vision and was later found to have small cell carcinoma of the lung. Complement-fixing antibodies reactive with retinal, optic nerve and cancer antigens was detected which may indicate an autoimmune cause for the vision loss.

Previous studies[13-15] on the clinical presentation of NPC, have reported cases of "visual loss", "impaired vision" and sometimes "optic nerve lesion". No mention of the exact aetiology was made and in most, tumour infiltration was presumed. Could this mean that optic neuropathy occurring as a paraneoplastic phenomenon in NPC be underdiagnosed? Hence, we would like to suggest that PON be considered in any patient who developed progressive visual loss in the setting of nasopharyngeal carcinoma. The realization that PON could be the initial manifestation of NPC and is recognised as such, would also lead to an earlier diagnosis and treatment and thus a better prognosis.


## ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of Dr Victor Yong, Dr S C Loong, Dr James Khoo, Professor S C Poh, Dr K A Abraham, Professor Y S Lee, Dr Elizabeth Cheah and Dr T H Khor who jointly managed this patient; and Dr Arthur Lim for his invaluable support.


## REFERENCES


1. Sawyer RA, Selhorst JB, Zimmerman LE, et al. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Opthalmol 1976;81:606-13.
2. Keltner JL, Roth AN, Chang RS. Photoreceptor degeneration: Possible autoimmune disorder Arch Opthalmol 1983;101:564-9.
3. Thirkill CE, Fitzgerald P, Sergott RC, Roth AM, Tyler NK, Keltner JL. Cancer-associated retinopathy (CAR Syndrome) with antibodies reacting with retinal, optic nerve and cancer cells. N Engl J Med 1989,321:1589-94.
4. Richter RB, Moore RY. Non-invasive central nervous system disease associated with lymphoid tumours. Johns Hopkins Med J 1968;122:271-83.
5. Lindenberg R, Walsh FB, Sacks JG. Neuropathology of vision. An Atlas. Philadelphia: Lea & Febiger, 1973:252-3.
6. Pillay N, Gilbert JJ, Ebers GC, Brown JD. Internuclear opthalmoplegia and optic neuritis: Paraneoplastic effects of bronchial carcinoma. Neurology 1984;34:78-91.
7. Boghen D, Sebag M, Michaud J. Paraneoplastic optic neuritis and encephalomyelitis: Report of a case. Arch Neurol 1988;45:353-6.
8. Henson RA, Urich H. Remote effects of malignant disease: Certain intracranial disorders. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. New York: Elsevier Science Publishing Co Inc, 1979;38:625-68
9. Fine RM. Autoimmune basis for visual paraneoplastic syndrome. Int J Dermatol 1985;24:509.
10. Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 1983;14:609-13.
11. Graus F, Cordon-Cardo C, Posner JB. Neuronal antinuclear antibody in sensory neuropathy from lung cancer. Neurology 1985;35:1438-42.
12. Dropcho EJ, Stanton C, Oh SJ. Neuronal antinuclear antibodies in a patient with Lambert-Eaton myasthenic syndrome and small cell lung carcinama. Neurology 1989,39:249-51.
13. Thomas JE, Waltz AG. Neurological manifestations of nasopharyngeal malignant tumours JAMA 1965;192:95-8.
14. Khor TH, Tan BC, Chua ET, Chia KB. Tumours of the nasopharynx-Singapore 1969-1971: The presenting picture. Singapore Med J 1975;16:236-43.
15. Godtfredsen E, Lederman M. Diagnostic and prognostic roles of opthalmoneurologic signs and symptoms in malignant nasopharyngeal tumours. Am J Opthalmol 1965;59:1063-9.