Radiation-induced neurological complications of nasopharyngeal carcinoma

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Abstract

Objectives: To review radiation-induced neurological complications of nasopharyngeal carcinoma (NPC). *Materials & Methods:* Retrospective review of patients with radiation-induced neurological complications of NPC who presented to the Neurology and Neurosurgery Departments, Tan Tock Seng Hospital in the five-year period from 1994 to 99. *Results:* Nine patients with 10 neurological complications were seen. Four patients had cranial nerve palsies, of whom two had optic atrophy, one had isolated third nerve lesion and another had combined third, fourth and fifth cranial nerve palsies. Three patients each had temporal lobe necrosis and cervical myelopathy. Two of the patients with temporal lobe necrosis presented with seizures while the third presented with syndrome of inappropriate anti-diuretic hormone secretion. Two patients with optic atrophy and another two with cervical myelopathy were treated with anticoagulation therapy. The patients with optic atrophy improved while the patients with cervical myelopathy stabilised. *Conclusions:* Radiation therapy for NPC may cause delayed neurological complications of cranial nerve palsies, temporal lobe necrosis and cervical myelopathy. Treatment with anticoagulation may be beneficial in patients with optic atrophy and cervical myelopathy.

Key words: nasopharyngeal carcinoma, radiation-induced injury, neurological complications, optic atrophy, cervical myelopathy, anticoagulation

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is relatively common in Southern China and South East Asia. The risk does not diminish among Chinese migrants outside this region and is highest in the Cantonese dialect group.[1] The incidence of NPC in Caucasians is less than 1 per 100,000 per annum whereas in Southern China it is 10-30 per 100,000 per annum. In Singapore, NPC was reported as the most common cancer among males aged 15 to 34 years. It was the sixth most frequent cancer from 1983 to 1987 and represented 5.6% of all cancers. The overall incidence was about 9 per 100,000 per annum with a male preponderance of 2.3 to 1.[2] As nasopharynx is close to the base of skull, 13 to 30% of patients with NPC have cranial nerve involvement during initial presentation.[3-5] Cranial nerve involvement may also be the first sign of tumour recurrence.

Radiotherapy is the primary treatment modality for NPC. It has been estimated that 10% of patients developed late neurological complications which occurred after a delay of many years, involving both the central and peripheral nervous system.[6] This is a retrospective review of NPC patients with delayed radiation-induced neurological complications seen in the Neurology and Neurosurgery Departments of Tan Tock Seng Hospital, over a 5-year period from January 1994 to January 1999. Tan Tock Seng Hospital is a general hospital in Singapore. The aim of the review is to determine the spectrum of the neurological complications and its outcome.

MATERIALS AND METHODS

All patients were evaluated by an otorhinolaryngologist and had histological confirmation of the NPC. They were given standard treatment protocols for their radiation therapy.[3] When indicated, repeat biopsies were performed to exclude tumor recurrence. All patients had computerised axial tomography (CT) scan and/or magnetic resonance imaging (MRI) of the head and neck. Two patients also had cerebral angiogram.

CT scans of the head were performed in the axial plane on a Picker 1200 spiral scanner. For the CT study, 5 mm thick sections of the posterior cranial fossa with 8 mm thick sections through the rest of the brain were obtained both before

and after the intravenous injection of 50 mls of contrast (Iopromide, 370 mg iodine/ml, Ultravist 370). CT examination of the post-nasal space (PNS) and neck entailed direct contrast enhanced three mm thick sections from the orbital roof till the junction of the second and third cervical spine with subsequent five mm thick sections till the junction of the seventh cervical spine and first thoracic spine. The skull base images were also processed and viewed using a bone algorithm.

The MRI studies were performed on a 1.5 tesla, General Electric Signa system. All scans were obtained both before and after intravenous injection of gadolinium contrast (Magnevist, 0.1 mmol/kg body weight) with spin-echo T1 and T2 weighted sequences. Typical MRI head examinations were done in the sagittal, axial and coronal planes using 5 mm slice thickness with two mm interslice gap. For the MRI of the PNS and neck, axial and coronal scans were obtained at three mm slice thickness and 1 mm interslice gap, with the T2 weighted and post-contrast T1 weighted scans done using fat saturation techniques. Pertaining to the problem of cervical myelopathy, scans were performed in the sagittal plane at three mm thickness, one mm interslice gap and in the axial plane at 5 mm thickness, one mm interslice gap.

RESULTS

Nine patients were seen, all were Chinese with 7 males and 2 females. The average age was 54 years. The average duration from their first diagnosis was 9 years (range: 1.5 to 17 years) and the average duration of neurological symptoms was 42 days (range: 1 to 180 days). Patient 5 presented on two separate occasions 5 years apart, first with seizures, then with a left optic atrophy. These were considered as two separate events in the analysis. The average duration of follow-up was three years. The demographics, clinical signs and radiological correlations are summarised in Table 1.

Four patients had cranial nerve palsies, of whom two had optic atrophy and one had isolated third nerve palsy. Another patient presented with a third nerve palsy which subsequently evolved to involve the fourth and sixth nerves on the same side. Three patients had temporal lobe necrosis with two presenting as seizures and one with confusion from hyponatraemia secondary to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Three others had cervical myelopathy. Six patients had other pre-existing neurological deficits with twelfth nerve palsy (4 patients), deafness (4 patients), sixth nerve palsy (one patient), ninth and tenth nerve palsies (one patient).

Patient #1 had NPC 10 years previously. She presented with a right painful complete third nerve palsy of one day's duration. An urgent cerebral angiogram was normal with no evidence of posterior communicating artery aneurysm. Post-nasal space examination revealed the presence of crust and atrophic mucosa. A biopsy done did not show any tumour recurrence. MRI scans however showed an enhancing mass at left post-nasal space infiltrating the skull base to involve both sphenoidal sinuses. The cavernous sinus was normal. A deep post-nasal and transphenoidal endoscopic biopsies of both sphenoidal sinuses showed inflammatory changes, focal necrosis and granulation compatible with radiation changes. There was complete recovery of the third nerve palsy ten weeks later. Patient 2 presented with right third, fourth and sixth cranial nerve palsies with recovery by 8 weeks.

Of the three patients with temporal lobe necrosis, one (Patient #3) had a right temporal-parietal lobectomy as metastasis was suspected. Histology revealed areas of necrosis and haemorrhage with no malignancy. The other two patients (Patient #4, 5) who presented with seizures had good response to anti-convulsants.

Two patients (Patient #5, 6) with optic atrophy and two (Patient #8, 9) with cervical myelopathy were anticoagulated with warfarin for an average duration of 2 years. Their international normalised ratios (INR) were kept between 1.5 and 2.5. Both patients with cervical myelopathy stabilised with no further deterioration. Patient 9 had MRI repeated at 3 months and 1 year, with complete resolution of the MRI changes. Both patients with optic atrophy showed improvement in visual acuity. The improvement was from 6/15 to 6/6 after one month in patient #5, and 6/12 to 6/6 after 6 months for patient #6. Both patients also showed improvement in their red colour vision. However, their superior altitudinal field defects persisted.

DISCUSSION

Lee et al reported that 31% of NPC patients developed one or more late radiation-induced sequelae. Of these, neurological complications occurred in 10% of patients accounting for the major cause of serious disability.[6] The present study demonstrated the variety of neurological

TABLE 1: Radiation-induced neurological complications of nasopharyngeal carcinoma

Patient No	Sex	Age	Duration from initial diagnosis	Neurological findings (new)	Neurological findings (old)	Radiological studies
1	F	60	10 years	right III	left VIII, IX, X	CT head: normal Cerebral angiogram: normal MRI: left postnasal mass invading skull base to sphenoid sinus; cavernous sinus, internal auditory canal, jugular fossa intact
2	M	66	17 years	right III, IV, VI	right conduction deafness	CT Head: normal Cerebral angiogram: normal MRI: changes at right pons, midbrain and left frontal lobe; cavernous sinus normal
3	M	68	6 years	confusion secondary to SIADH		CT: right temporal lobe necrosis MRI: right temporal lobe necrosis (Fig 1)
4	M	54	15 years	fits	right XII	CT: left temporal lobe necrosis MRI: left temporal lobe necrosis
5	M	40	6 years	fits	bilateral XII, left conduction deafness	MRI: left temporal lobe necrosis optic nerves normal
		45	11 years	left optic atrophy	bilateral XII left conduction deafness	MRI: left temporal lobe necrosis
6	M	54	8 years	left optic atrophy		CT: no skull base erosions, optic nerves intact
7	F	55	14 years	right C5,6 cervical myelopathy	bilat VI bilat XII	MRI spine: no tumour recurrence or cervical cord abnormalities; livus and upper cervical spine show post-radiation fatty marrow
8	M	58	2 1/2 years	cervical myelopathy		MRI spine : radiation myelitis from C1-4 level; post radiation fatty marrow at clivus and upper cervical spine
9	M	36	1 1/2 years	cervical myelopathy		MRI spine : radiation myelitis at C1,2 level; post-radiation fatty marrow at clivus and upper cervical spine (Fig 2a & b) Repeat MRI 3 months and 1 year later : cervical cord normal

M = male, F = female. Unless otherwise specified, 'CT' refers to CT scan of the head and neck, and 'MRI' refers to MRI of the head and neck

problems that may occur from the radiation therapy. Although cranial nerves are relatively resistant, radiation-induced cranial nerve palsies have been reported with an incidence ranging from 0.3 - 6 %.[6-8] Four of our patients suffered cranial nerve palsies of which two had optic atrophy, one had isolated third cranial nerve palsy and another with combined third, fourth and sixth cranial nerve palsies. While radiation-induced third nerve palsies have been reported with other tumours[9], this is the first report of third nerve paralysis related to radiation therapy in NPC. However, ocular neuromyotonia of the third cranial nerve has been reported, with delayed relaxation of extraocular muscles from tonic discharges.[10] The cause of radiation-induced cranial nerve palsies has been attributed to vascular damage or fibrosis.[11] Direct nerve injury while possible probably occurred very rarely.[12]

The last four cranial nerves, particularly hypoglossal nerve, have been found to be the most commonly affected cranial nerve in the literature.[6,13,14] Five of our patients were found incidentally to have lower cranial nerve palsies. They were not included in the analysis as the deficits were pre-existent.

Temporal lobe necrosis has been reported to occur in up to 3% of patients after radiotherapy.[6] This occurs as the inferomedial portions of the temporal lobes lie directly within radiation ports. Three of our patients had radiological evidence of temporal lobe necrosis (Fig. 1). Although the condition is potentially life-threatening, our patients had good prognosis. While corticosteriods have been advocated to treat cerebral edema[15], none of our patients required such therapy.

Delayed cervical spinal cord radiation-induced myelopathy was said to occur in 1-2% of patients.[6,16] MRI of the cervical spine revealed radiation myelitis with swelling, oedema and enhancement at the upper cervical cord in two out of three of our patients. All three patients showed post-radiation fatty marrow signals at the clivus and upper cervical spine (Fig. 2a & b).

Glantz et al[17] has shown that anticoagulation may be beneficial in radiation-induced injuries in patients with temporal lobe necrosis, myelopathies and plexopathies. The hypothesis was that this would arrest and reverse small vessel endothelial injury which may be the fundamental lesion of radiation necrosis. On the other hand, Landau & Killer[18] reported a patient
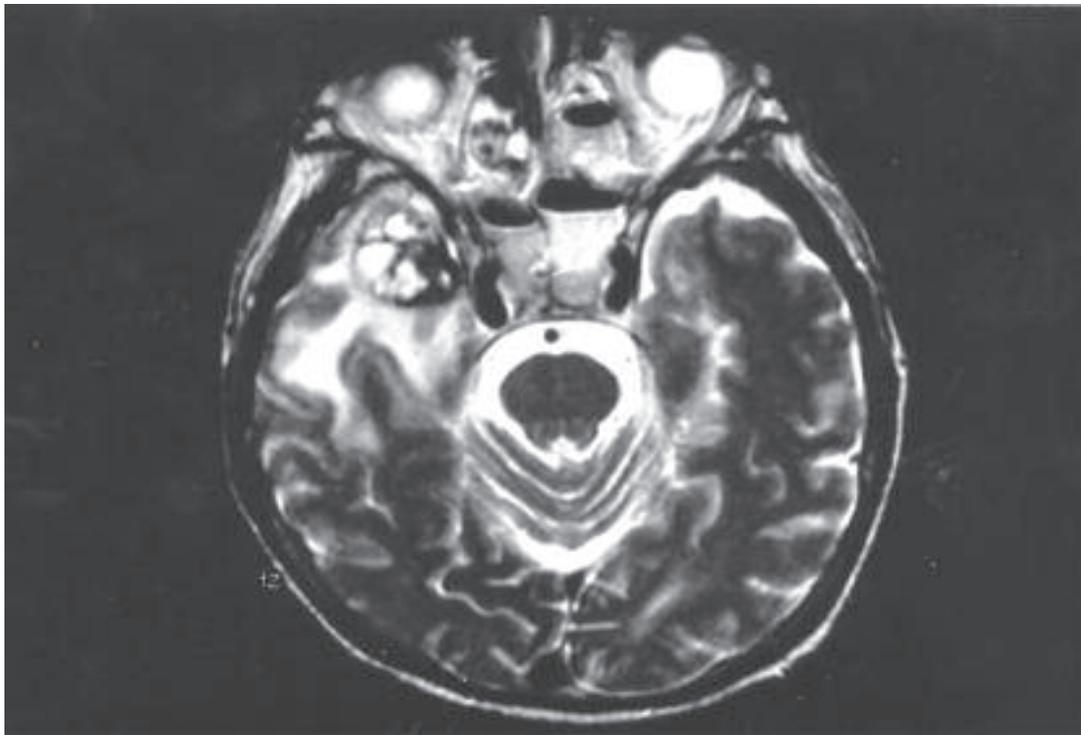

FIG. 1: MRI of Patient 3 showing right temporal lobe radionecrosis with foci of calcification, haemorrhage and white matter oedema on T2 weighted image.
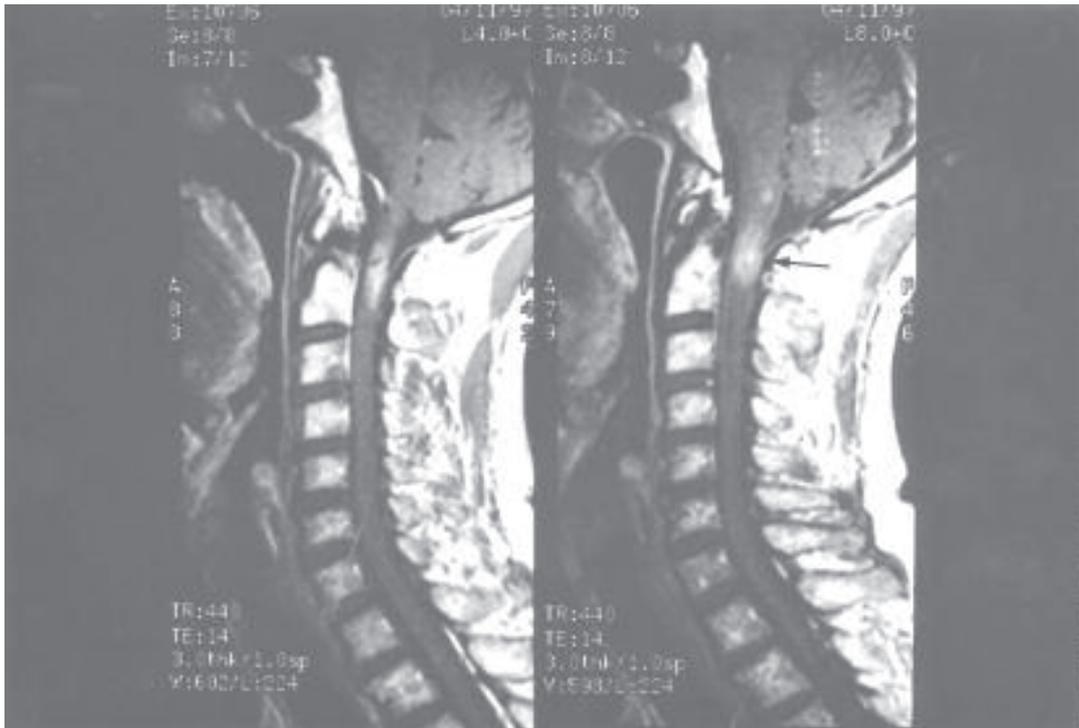
Fig 2a: MRI of Patient 9 showing radiation myelitis with enhancement of the cervical cord at C1-2 level (arrow).
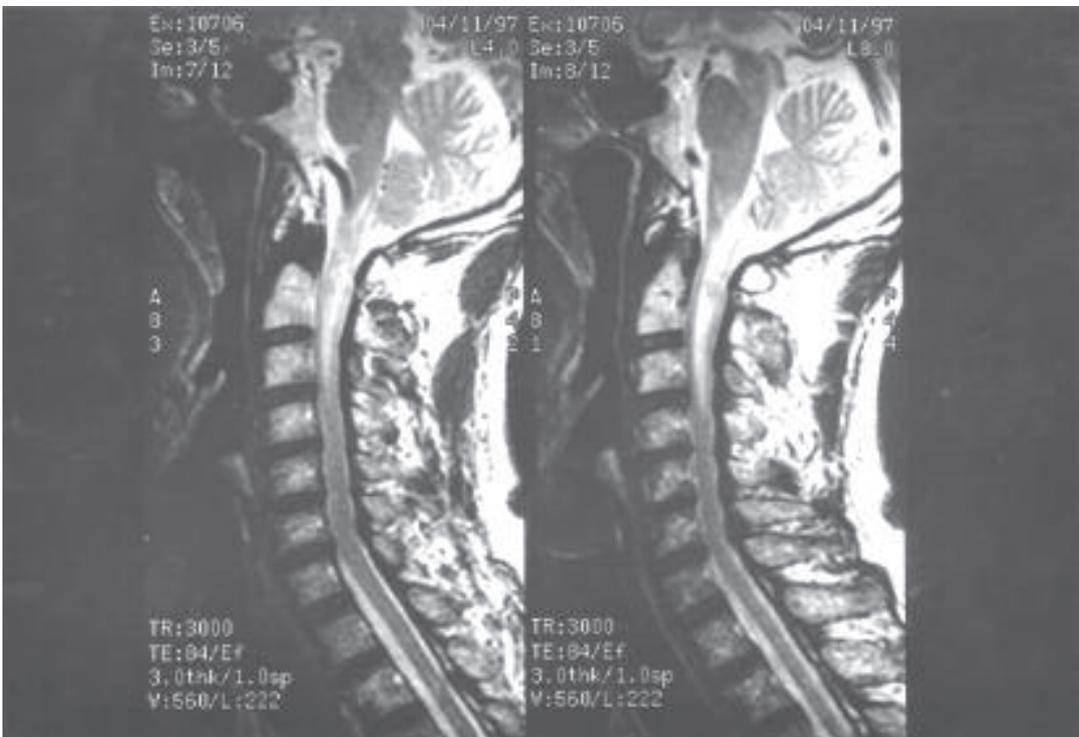

Fig 2b: Swelling and oedema of the upper cervical cord, hyperintense fatty marrow at the clivus and upper cervical spine.

who while on anticoagulation for high-grade right internal carotid stenosis received radiotherapy for pituitary adenoma. The patient developed radiation-induced optic atrophy nine months after treatment despite being anticoagulated during and after radiotherapy. Our patients, including two with optic atrophy have apparently benefited from the anticoagulation therapy, with stabilization and improvement of their neurological deficits. There has been no other reported radiation-induced optic atrophy treated by anticoagulation in the literature. A prospective controlled study is needed to further assess the role of anticoagulation in radiation-induced nervous system injuries.

The total dose of radiation and fraction size are important factors in the development of post-radiation complications. Lee et al demonstrated that patients receiving a reduced fractional dose were less likely to develop temporal lobe necrosis.[19] Advances in radiology to better delineate tumour extent and improved shielding of normal tissues are possible means to further reduce radiation related neurological complications in the future.

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