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Factors contributing to delayed diagnosis in nasopharyngeal carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) can be difficult to diagnose. Not only is the post-nasal space (PNS) inaccessible to examination, it is frequently occupied by normal lympho-epithelium which can make differentiation from NPC difficult. Together with its frequent atypical presentation, it is not surprising that the diagnosis is missed or delayed. This is undesirable as the treatment of early NPC carries an excellent prognosis. The aim of this study is to ascertain the extent of the problem of missed or delayed diagnosis and to study the factors responsible.

This was a retrospective study of all newly diagnosed patients with NPC from the Singapore General Hospital and treated in the Department of Therapeutic Radiology in the year 1996 (1 January-31 December).

A total of 126 patients were studied. Eighteen patients (14.3 per cent) were found to have delayed diagnosis of more than a month. The delay ranged from 1.2 to 25 months (mean 7.2 months). Factors identified which contributed to delayed diagnosis included i) Clinicians not considering a diagnosis of NPC ii) Clinicians suspecting NPC but misled by the results of investigations iii) Patients refusing investigation or defaulting follow-up.

Nearly a fifth of patients with NPC had delayed diagnosis. Many of the factors responsible for the delays appear to be preventable by better patient education and counselling, doctors having sharper clinical acument and skills in NPC diagnosis and the hospital administration having a system of tracking down high risk patients who default.

Key words: Nasopharyngeal neoplasms; Carcinoma; Diagnosis

Introduction

Nasopharyngeal carcinoma (NPC) is a common disease among the Chinese in Singapore with an incidence of 18.1 and 7.4 (age-standardized rate per 100,000 per year) for males and females respectively (Chia *et al.*, 1996). The main modality of treatment i.e. radiotherapy has excellent results in patients with early cancers, with up to 90 per cent of patients with Stage 1 disease having a five-year survival. However, the early diagnosis of NPC can be a difficult task because the PNS is relatively inaccessible to examination and the frequent presence of normal lympho-epithelium makes an accurate diagnosis even more difficult (Low, 1997). This is compounded by the fact that the presentation of NPC is variable and patients consult doctors of different specialities who had have little experience in managing NPC. It is, therefore, not surprising if the diagnosis of NPC in a patient is missed or delayed. The aim of this paper is to ascertain the extent of the problem of missed/delayed diagnosis and to study the factors responsible for it.

Methods and materials

The case records of all newly diagnosed patients with NPC from the Singapore General Hospital treated in the Department of Therapeutic Radiology in the year 1996 (1 January–31 December) were studied. The patients were seen initially by various departments of the Hospital, namely Otolaryngology, General Surgery, Respiratory Medicine and Oncology. The length of time taken to diagnose NPC is calculated from the date of first consultation with any clinician of the Hospital for symptoms related to NPC to the date when histological confirmation is obtained.

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Results

A total of 126 patients were studied. One hundred and eight patients (85.7 per cent) were diagnosed within one month from the first date of consultation. Of these, 91 patients (72.2 per cent) were diagnosed within two weeks. Those who were not diagnosed within four weeks were considered to have delayed diagnosis in this study. A period of four weeks was deemed as sufficient to allow for logistical delays and any additional or repeat tests which may be required to clinch the diagnosis in some cases. Eighteen (14.3 per cent) patients were found to have delayed diagnosis. The length of time taken to come to a diagnosis for these 18 patients ranged from 1.2 to 25 months (mean 7.2 months). These cases were further analysed to identify the factors contributing to the delay in diagnosis (Table I). As shown in the table, these factors were categorized as clinician- or patient-related factors. Although each patient may have several factors contributing to a delay in diagnosis, only the main factor for each patient was considered. The main factor being the one that caused the longest lapse in diagnosis.

Clinician factors

The delay period ranged from 1.2 to 25.0 months (mean 7.6 months).

(i) NPC not considered at initial presentation (five patients).

These included patients who presented with atypical signs and symptoms. One had cervical, axillary lymphadenopathy and hepatomegaly resulting in a working diagnosis of lymphoma. Another patient presented with impaired vision of the left eye. Computed tomography (CT) scan showed a left orbital apex lesion. Biopsy of the lesion showed undifferentiated carcinoma and it was only then that NPC was suspected. Another patient presented with a parapharyngeal abscess, which was later shown to be a result of metastatic NPC. The fourth patient presented with purulent nasal discharge with facial pain and a clinical diagnosis of sinusitis was made. He was subsequently found to have NPC involving the ethmoid/sphenoid sinuses. The last patient, who presented with left cervical lymphadenopathy of two months duration was initially seen in a non-otolaryngologic unit. The first attending clinician failed to perform a PNS examination but did a fine needle aspiration cytology (FNAC) of the node instead. The result was positive for malignancy and a lymph node biopsy then obtained showed metastatic undifferentiated carcinoma. Only then was the PNS examined and biopsied to confirm NPC.

TABLE I

SHOWING THE MAIN FACTOR IN EACH PATIENT WHICH LED TO DELAYED DIAGNOSIS

		No. of Cases
Clinician factors	NPC not suspected	5
	NPC suspected but dismissed	7
Patient factors	Refused investigations	2
	Defaulted	4
Total		18

(ii) NPC considered at initial presentation but dismissed (seven patients)

There were five patients in whom NPC was considered as a possible diagnosis at initial presentation but was dismissed because examination of the PNS was thought to have no tumour. In another patient with cervical lymphadenopathy, the PNS was noted to be unremarkable, and FNAC showed 'necrotic material'. The node persisted and subsequent excision biopsy almost three months later showed metastatic NPC. In a patient who presented with nasal blockage and an unremarkable looking PNS, although EBV serology titres were found to be raised, PNS biopsy showed only chronic inflammation. The patient was observed and it was only approximately three months later that a repeat biopsy was performed which confirmed NPC.

Patient-related factors

The delay period ranged from 1.5 to 11.0 months (mean 5.8 months).

i) Patients who refused further investigations (two patients).

The first patient presented with cervical lymphadenopathy and the PNS examination was unremarkable. FNAC of a cervical node showed reactive lymphoid hyperplasia. The clinician immediately suggested performing excision biopsy of the cervical node but the patient refused and instead opted to observe the lymph node. Finally, after observation for three months, cervical lymph node biopsy was done which showed metastatic undifferentiated carcinoma. The second patient also had cervical lymphadenopathy. The FNAC of this patient revealed metastatic undifferentiated carcinoma. She refused PNS biopsy under local anaesthesia as she was apprehensive of the procedure. PNS biopsy was finally done under general anaesthesia but only after three weeks because of logistical delays.

ii) Patients who defaulted (four patients).

Of the four patients who defaulted, one did not return on the appointed date after a PNS biopsy which was subsequently proven to be positive for NPC. Another patient did not keep his appointment with the otolaryngologist after being referred by a non-otolaryngologist who made a provisional diagnosis of NPC. The last two patients were found to have suspicious PNS masses, but their clinicians chose to do EBV screening before deciding on biopsies of the PNS lesions. Unfortunately, the patients defaulted even before the results (which were positive) were made known to them.

It must be pointed out that only the main contributing factor for each patient has been considered so far. There are other contributing factors in some patients and these included factors relating to:

a) EBV serology. Two patients who had EBV IgM instead of EBV IgA serology done. Both the results were negative. As EBV IgM has no predictive value in NPC, it misled the clinicians in both cases into considering them as having low risks for NPC. In another two patients, EBV IgA serology for VCA was only slightly raised but that for EA was negative. These results lowered the clinicians' indices of suspicion for NPC which resulted in the patients being observed for a further 1.75 and four months respectively before PNS biopsies were carried out.

b) PNS biopsy results. There were also patients whose diagnosis were delayed by PNS biopsy results such as 'blood', 'chronic inflammation', 'acute on chronic inflammation' and 'negative for malignancy'.

c) FNAC results. Four patients were delayed by inconclusive FNA results. Results obtained include, 'reactive lymphoid hyperplasia', 'necrosis', 'insufficient yield for diagnosis', 'atypical cells in reactive lymphoid background'.

Discussion

In the assessment of patients suspected of having NPC in our Department, a detailed history is taken with special attention to both ear and nose symptoms. A thorough physical examination is carried out with emphasis on nasopharyngoscopic finding of the PNS. Any suspicious area is biopsied (local anaesthesia) under endoscopic guidance. A sample of blood is then taken at the same sitting for EBV IgA serology to support the diagnosis of NPC. If the clinical suspicion for NPC is high, random biopsies of the PNS (local anaesthesia) may be done, assisted by computed tomography (CT) scans of the area. In certain cases where the clinical suspicion for NPC is high and yet investigations yield negative PNS biopsies under local anaesthesia, deep biopsies/PNS curettage under general anaesthesia may be performed. In a patient presenting with cervical lymphadenopathy, FNAC is performed if the PNS examination is normal.

Clinician-related factors

Diagnosis of NPC has always been a great clinical challenge because i) it is a great masquerader of symptoms of many diseases and continues to deceive even the most experienced clinician ii) the nasopharynx is a difficult region to assess with wide variations of normality iii) NPC is often inconspicuous in the PNS and is not uncommonly missed and iv) the current investigative tools in use have their limitations which can mislead the clinician. The clinician should always be mindful of:

A) The unusual presentation.

The common signs and symptoms of NPC are those related to the neck, ear and nose. There remain a small but significant group of patients who do not display such obvious signs and symptoms. The bizarre and confusing nature of this disease has misled clinicians and contributed to delayed diagnosis in five out of 18 patients studied (Skinner and Van Hasselt, 1991). We have to bear in mind that about five per cent of patients have distant metastasis and one in five of these has multi-organ deposits at the time of first presentation (Neel and Taylor, 1983). Delay in diagnosis could possibly be avoided by simple PNS examination upon first consultation.

B) The 'normal' post-nasal space.

Inspection of the PNS is a subjective assessment where a PNS appearing normal to one clinician may appear abnormal to another. This is exacerbated by the wide range of normality of the PNS, the often subtle signs of NPC and the different methods used to examine the PNS such as using the mirror or nasal endoscope. Furthermore, in six to 10 per cent of patients, the PNS tumour is submucosal and the mucosa may appear entirely normal (Woo and Waldron, 1991). As illustrated in this paper, the clinician has to be wary of dismissing a diagnosis of NPC just because the PNS appears 'normal'. All factors have to be considered before an index of suspicion for NPC is derived. If the index of suspicion is sufficiently high, appropriate steps must be taken immediately to exclude the disease.

C) Negative investigation results.

It is important to keep in mind the possibility of false negative or inconclusive results in tests for the diagnosis of NPC.

(i) PNS biopsy. PNS biopsy can be performed under local anaesthesia in the office under endoscopic guidance and we must be mindful that false negative results can occur. The sensitivity of initial biopsy using this technique in diagnosing NPC was 95.1 per cent and a predictive negative value of 96.4 per cent has been reported by Waldron *et al.* (1992). In another study, 8.1 per cent of the biopsy findings were negative in the presence of an exophytic PNS tumour and this occurred in 31.9 per cent of all patients (Sham *et al.*, 1989). A superficial biopsy may not include tumour cells as NPC may be endophytic and spread submucosally (Sham *et al.*, 1989). The experience and familiarity of the clinician in the technique of biopsy plays an important role in improving the yield of positive results.

(ii) FNAC of cervical lymph node. FNAC is an efficient and cost-effective modality of obtaining histological specimens. Its main advantage is that it is easy enough to be performed in any clinic and well-tolerated by many patients. Of the cases studied in this paper the diagnosis for four patients were delayed by inconclusive FNAC results. Three patients eventually then underwent lymph node biopsy and one had FNA performed again that

clinched the diagnosis. The inadequacy rate of lymph node FNAC in the Singapore experience was quoted by Kaur *et al.* as 14.6 per cent and the cytology: histology accuracy rate was 82.6 per cent (Kaur *et al.*, 1994). To ensure a low inadequacy rate, it is important to have doctors who have been trained in FNAC, together with a trained cytology technician to assist the doctor with smear and staining. It must be stressed that the PNS must be examined first before attempting this procedure. Failure to do so would subject the patient to unnecessary biopsies and yet find the primary wanting.

(iii) Epstein-Barr virus (EBV) serology. EBV is closely associated with NPC, in particular the viral capsid antigen (VCA) and early antigen (EA) are good markers for diagnosis of NPC (Chan, 1997). More than 90 per cent of NPC patients have elevated antibodies to EBV determinant antigens (Chew, 1990). In our institution, the EBV serology is done with EBV-B95-8 antigen using the immunofluorescence assay (Chan, 1997). EBV anti-VCA and EA have to be read in combination as this gives better results in screening for early cases (Liu *et al.*, 1997). As 'negative' titres for anti-VCA and anti-EA can be found in 18.8 per cent and 20 per cent of NPC patients respectively (Kaur *et al.*, 1993), patients should not be dismissed as not having NPC based on serology alone.

Patient-related factors

Patient-related factors were found to account for about one-third of the main reasons for delayed diagnosis. While it is difficult to ascertain precisely the reasons for patients wanting to default follow-up with the clinicians, some postulations can be made. Firstly, education and proper counselling of patients may be lacking. There is a tendency among clinicians to trivialize a patient's condition before a firm diagnosis is made so as not to alarm the patient (Van Hasselt and Skinner, 1990). This practice may unwittingly contribute to patients defaulting follow-up. The chances of default are also increased if the importance of early diagnosis and the good results of treatment in early tumours are not stressed during the counselling sessions. It is interesting to note that three out of the four patients who defaulted did not even bother to turn up to find out the outcome of their investigation results. Although the results were abnormal, there was no tracking mechanism in place to make proactive efforts to recall the patients after they had defaulted. Secondly, traditional medicine is widely practised in Singapore and is firmly believed by many to be effective. This may have contributed to the high default rate as patients turn to practitioners of traditional medicine for a second opinion. It should be pointed out that for one patient who chose to refuse further investigations, the negative FNAC results appears to have given the patient a false sense of security. The clinician therefore, should be mindful of such an outcome and avoid performing unnecessary investigations if the diagnosis can easily be clinched by a biopsy of an obvious PNS lesion.

Conclusion

Nearly one-fifth of patients with NPC have delays in diagnosis. Both patients- and clinician-related factors feature in such delays. However, these may be minimized by patients being given better education and counselling, the clinician having sharper clinical acumen and skills in diagnosing NPC and the hospital administration having a system of tracking down high risk patients who default.

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