

ORIGINAL STUDY

Diagnostic particularities of advanced nasopharyngeal carcinoma

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ABSTRACT

BACKGROUND. Nasopharyngeal carcinoma (NPC) is a disease in which malignant cells develop in the tissues of the nasopharynx. NPC is frequently misdiagnosed due to its anatomical position and the common symptoms that appear in disease's natural history.

OBJECTIVE. The aims of the study were: to identify the particularities in the diagnostic of patients with advanced carcinoma, the most frequent onset symptoms or syndromes and the time elapsed from onset of first NPC symptoms to diagnosis and treatment.

MATERIAL AND METHODS. The authors present their experience in evaluating and diagnosing patients with NPC in a 2 years retrospective clinical study which included 54 patients. The evaluation protocol consisted in: clinical examination, nasal endoscopy, fiberoptic laryngeal assessment and otoscopic exam, pure-tone audiometry and tympanogram. Details about symptoms and their onset, the time elapsed before the first doctor evaluation or previous treatments were taken into consideration.

RESULTS. From all 54 patients included in the study, 38.88% waited 6 months to 1 year till the first symptom onset to seek for medical advice and 33.33% between 3 and 6 months. The patient's symptoms often included nasal obstruction (38.88%), blocked ear sensation or decreased hearing (33.33%) and cervical tumour masses (11.11%). Over 50% of the patients were diagnosed with NPC stage III and IV.

CONCLUSION. Nasopharyngeal carcinoma is often diagnosed in advanced stages due to its epidemiology, pathology and clinical presentation. In Romania, over 50% of the patients with newly diagnosed NPC present with locally advanced, or metastatic, stage III or IV disease due to the poor medical education of the population. Due to its very wide spectrum of symptoms, a high degree of suspicion from the ENT specialist and an increased awareness of the patient are crucial for the recognition of an early lesion.

KEYWORDS: nasopharyngeal carcinoma, locally advanced nasopharyngeal tumour

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumour originating from the epithelium of the nasopharynx. It represents a unique form of head and neck cancer poorly understood and commonly misdiagnosed, especially due to its specific behaviour (particular epidemiology, natural history and therapeutic considerations).

Patient's symptoms fit into four general clinical types: aural, nasal, neck and neurologic (cranial nerves involvement). Patients with early stages of the disease may present ear-related complaints. Middle ear effusion (hear-

ing loss, ear blockage sensation or otalgia) is a common otological manifestation of NPC and may be the only presenting symptom of the disease¹. Referred otalgia with a normal otoscopy could raise suspicion for a NPC involving the IXth cranial nerve¹. Middle ear or auditory nerve involvement can lead to tinnitus, which is highly unlikely to be an isolated symptom but a possible one according to van Hasselt and Gibb¹. The nasal symptoms are: nasal obstruction, rhinorrhea and recurrent epistaxis. Frequently, the first symptom is a cervical mass – according to Neel and Dickson, 60 to 70% of patients presents to the ENT specialists for cervical adenopathy².

Cranial nerve involvement is manifested by isolated nerve palsies or anterior or posterior syndromes. Anterior syndromes are clinical manifestation of the lesions affecting the middle cerebral fossa nerves:

- The superior orbital fissure syndrome: involves CN III, IV, VI, ophthalmic branch of the trigeminal nerve and superior ophthalmic vein. Clinical manifestations are: total ophthalmoplegia, pain/paresthesias/sensory loss in V1 area, proptosis/chemosis/lid edema; pupil is mydiatric and fixed³;
- Orbital apex syndrome (OAS): involves CN II, III, IV, V1, VI. Patients suffering with this syndrome have complete ophthalmoplegia, ptosis, decreased corneal sensation and visual loss⁴;
- Jaccoud syndrome is characterized by progressive ophthalmoplegia, trigeminal neuralgia and neurosensorial loss³;
- Gradenigo syndrome affects CN V and VI with facial pain/numbness, retroorbital pain, abducens nerve palsy (impairment of lateral movements of the eyeball) and otorrhea³;
- Reader syndrome involves CN V, VI and sympathetic cervical nerve: impairment of lateral movements of the eyeball and pain/paresthesias/sensory loss in trigeminal nerve area and manifestations of Claude-Bernard –Horner syndrome – ptosis, miosis without anhidrosis, and ipsilateral head/facial/retroorbital pain³.

Posterior syndromes are found in NPC that involves the skull base or in those cases with bulky upper cervical nodes (CN XII) or the jugular foramen involvement (CN IX, X, XI)²:

- Vernet syndrome: CN IX, X, XI palsies
- Villaret syndrome involves CN IX, X, XI, XII and Claude-Bernard-Horner syndrome
- Garcin syndrome – are found CN form I to XII – intracranial hypertension
- Trotter syndrome⁵

At their first ENT assessment, patients usually have advanced local disease, which includes stages ranging from T2b N0 to T4 N3⁶. NPC is often highly infiltrated and heterogeneous in all disease stages.

Unfortunately, in Romania nasopharyngeal carcinoma is a disease frequently diagnosed in advanced stages. As in any other country this feature is due to population's poor medical education. Also, it is very well known that in early stages NPC symptoms are not severely affecting patients' quality of life. Symptoms like nasal obstruction, rinorrhea, sensation of ear blockage, progressive hearing loss are not taken seriously by the patient. The consequence is the delay between the presenting symptoms and diagnosis moment.

MATERIAL AND METHODS

We performed a 2 years retrospective clinical study (January 2011 – December 2012) on 54 patients admitted in our Department and diagnosed with nasopharyngeal carcinoma. 42 men and 12 women were included in the study, with male:female ratio of 3.5 to 1 (Chart 1). Patient's ages varied from 12 to 72 years old (Table 1).

The diagnosis protocol used in all patients included: clinical evaluation, nasal endoscopy, fiberoptic laryngeal assessment and otoscopic exam, pure-tone audiometry and tympanogram. Details about symptoms and their onset, the time elapsed till the first doctor evaluation or previous treatments were taken into consideration. In all cases we tried to establish the disease staging.

The aims of the present study were:

1. To identify the particularities of those cases with advanced nasopharyngeal carcinoma;
2. To identify the most frequent presenting symptoms or syndromes;
3. To establish the time elapsed from onset of first NPC symptoms to diagnosis and treatment.

RESULTS

Analyzing the data obtained we found that the most frequent symptoms related by the patients were nasal

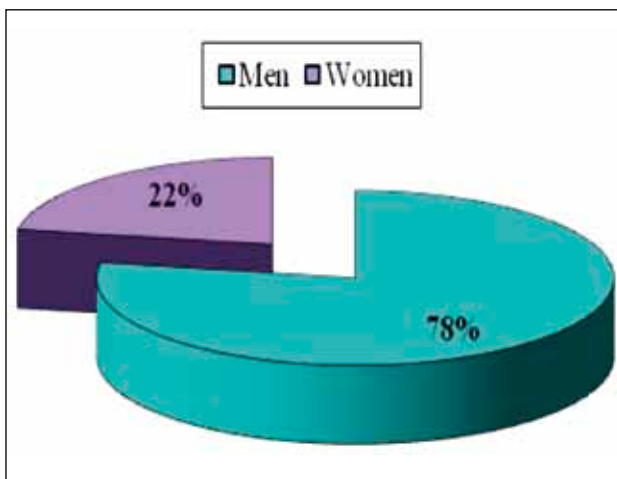


Chart 1 Patients' sex distribution in the study group

Table 1
Age repartition in the study group

Age	10 – 20	20 -30	30 – 40	40 – 50	50 – 60	60 – 70	70 - 80
Patients	3	3	15	6	12	9	3

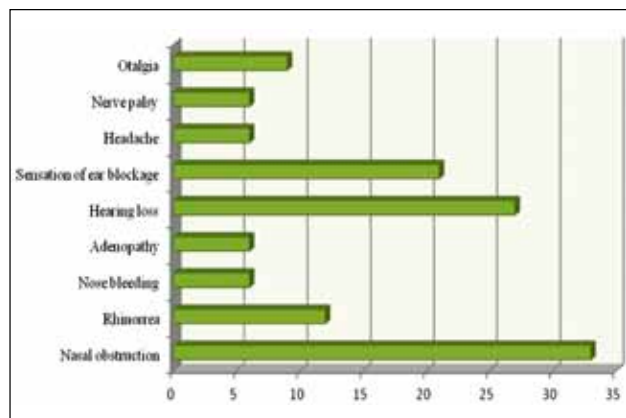


Chart 2 Frequency of first symptoms in NPC

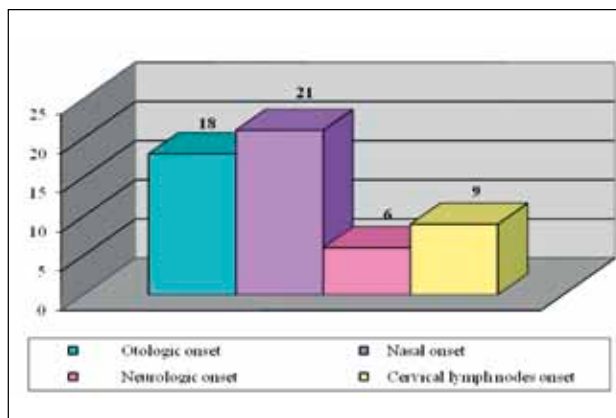


Chart 3 Onset type in nasopharyngeal carcinoma

obstruction (61.11% of the cases), hearing loss (50%) and blocked ear sensation (38.89%) (Chart 2).

If we consider the onset of the nasopharyngeal carcinoma, 38.88% of the patients presented with nasal symptoms, 33.33% with otological symptoms and 16.66% with cervical adenopathy. 11.11% related as bothersome symptoms cranial nerve disorders (palsies) (Chart 3).

Counting the time elapsed from the presence of first symptoms and patients' first medical assessment, 38.88% of the patients included in our study waited 6 months to 1 year to seek for medical advice, while 33.33% between 3 and 6 months. Patients with hearing loss were the first ones who presented for a medical check-up.

Regarding the tumour stage at the diagnosis, almost 50% of our patients performed their first medical visit in advanced stages of disease – 33.35% were diagnosed with NPC in stage IV (27.78% IVA, 5.57% IVB) and 16.66% in stage III. 38.88% of the cases were diagnosed in the first stage of disease (Chart 4).

Unfortunately, in some cases the patients were evaluated by several ENT specialists before the correct diagnosis was established.

To illustrate our study results and the stage in which over 50% of the Romanian patients with nasopharyngeal carcinoma present to the doctor, we have chosen to present some of the most representative cases.

Case 1

A 57-year-old man presented to our Department for persistent dysphonia (hoarseness), dysphagia and left cervical mass tumour, with almost 2 months onset.

3 weeks earlier the patient was admitted in another ENT service where he was investigated (direct laryngoscopy, esophagoscopy, cranial MRI, chest CT-scan) and diagnosed with nasopharyngeal tumour. A biopsy was taken, but the histopathologic result was inconclusive and the patient was discharged.

Clinical examination revealed a left cervical tumour mass of 2/1.5cm, with a relatively hard consistency, mobile on deep and superficial plans, slightly painful on

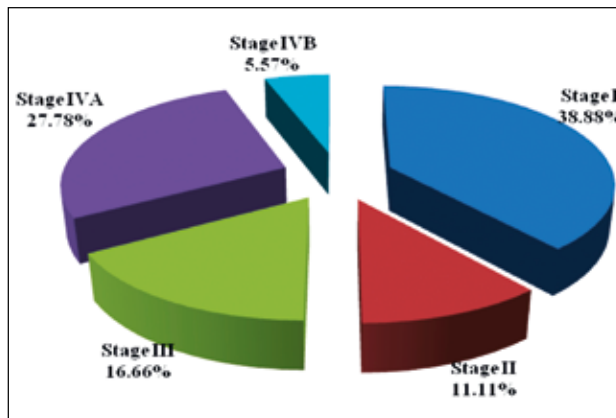


Chart 4 NPC staging on diagnosis



Figure 1 Laryngofibrosopic examination – infiltrative tumour arising from the left supero-postero-lateral wall of the nasopharynx, covered with mucous secretion

palpation. The laryngofibrosopic examination showed an infiltrative, red tumour arising from the left supero-postero-lateral wall of the nasopharynx (Figure 1) and left vocal cord palsy in paramedian position with salivary stasis in ipsilateral pyriform sinus.

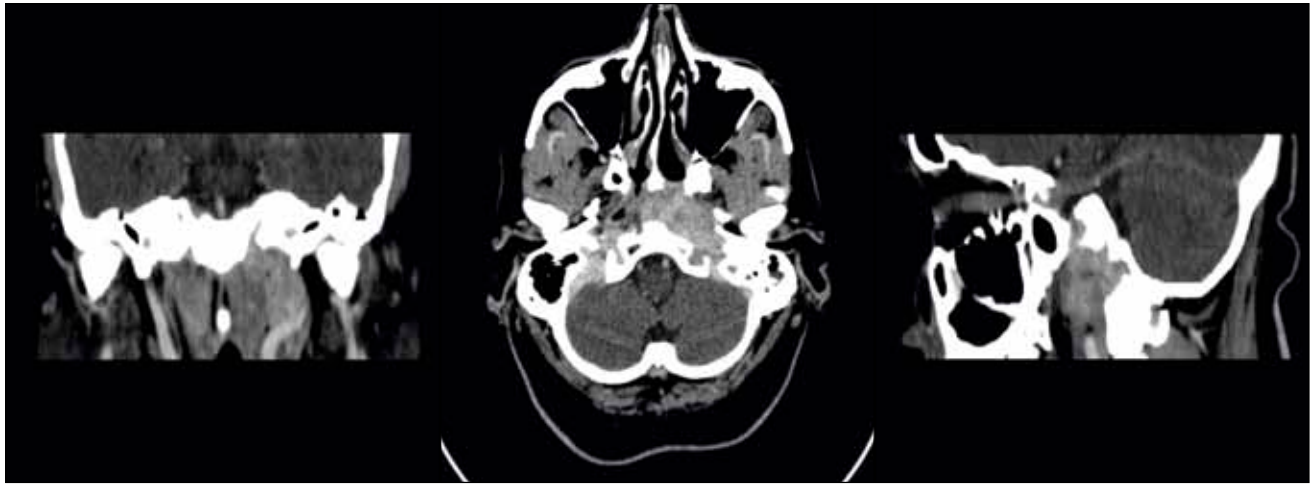


Figure 2 Cranio-facial CT-scan (coronal, axial and sagittal slices) - nasopharyngeal mass arising from the 2/3 of the postero-superior lateral left wall, with invasion of the parapharyngeal, retropharyngeal and prevertebral spaces, extended on the left Eustachian tube.

The cranio-facial CT-scan (Figure 2) described a nasopharyngeal mass arising from the 2/3 of the postero-superior lateral left wall, with invasion of the parapharyngeal, retropharyngeal and prevertebral spaces, extended on the left Eustachian tube. The tumour invaded the left carotid canal embedding the internal jugular vein and the common carotid artery, compressing and including the V, IX, X, XI, XII nerves; eroding the left occipital condyle, petrous bone, infero-lateral part of the clivus and penetrating the left sphenoid sinus

Fiberoptic laryngeal assessment, oesophagus examination and the chest CT scan revealed no other lesions.

A biopsy under endoscopic control was performed, the histopathologic result being nonkeratinizing nasopharyngeal cell carcinoma. When diagnosed the tumour stage was IVA.

The particularity of this case consists in the fact that the patient presented to the doctor relatively early, 2 months after symptom's onset, but he was misdiag-

nosed, because the first biopsy was superficial and revealed only the mucosal inflammation.

Interesting in this case were also the symptoms for which the patient addressed to us: hoarseness and dysphagia. Both symptoms range though within neurological debut, in this case speaking about nerve X palsy. Correlating clinical data with the CT-scan we expect the patient to develop a Collet-Sicard syndrome.

Case 2

A 67-years-age female was admitted in our Department relating nasal obstruction, antero-posterior purulent rhinorrhea, otalgia, blocked ear sensation and left side hemicranias. Symptoms started 5 months before and had a progressive evolution.

Clinical evaluation and endoscopic exam revealed voluminous red tumour mass occupying more than 2/3 of nasopharynx mostly on the left side; the same aspect was found on the left nasal

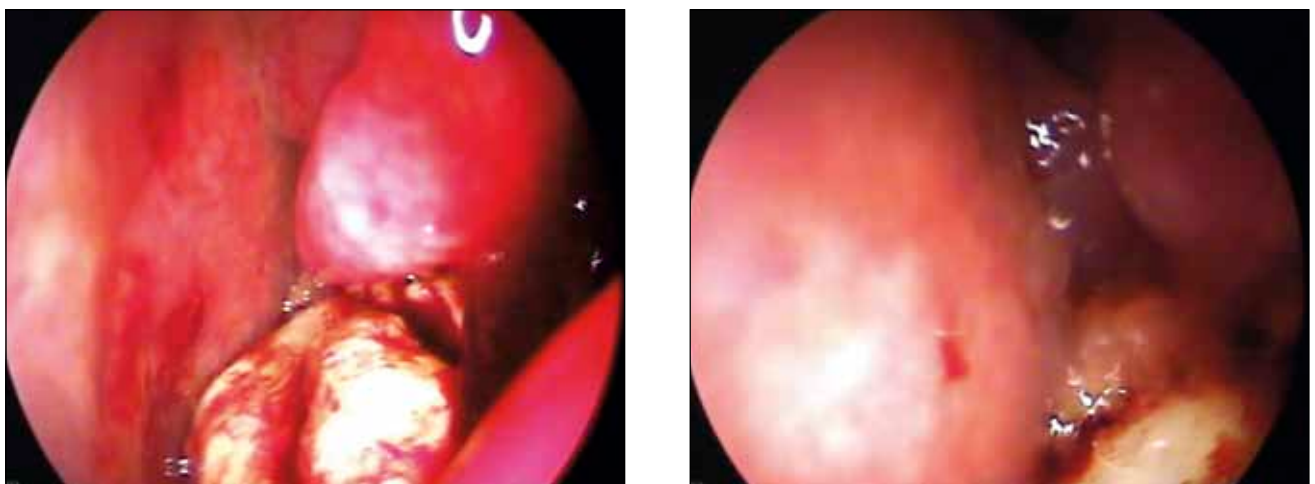


Figure 3 Nasal endoscopic examination – red, pulsatile tumor originating from the left middle meatus

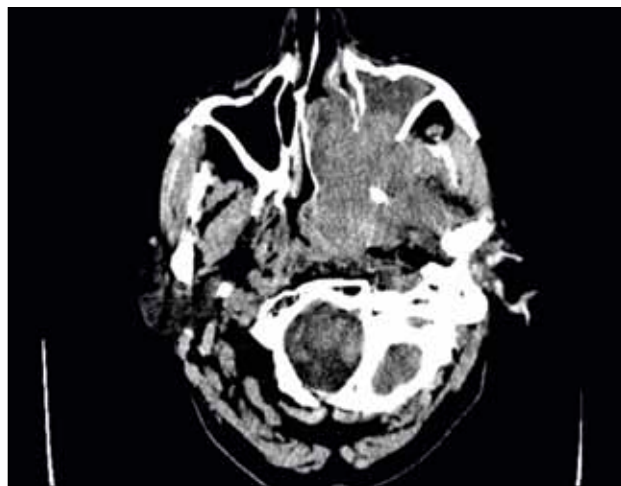
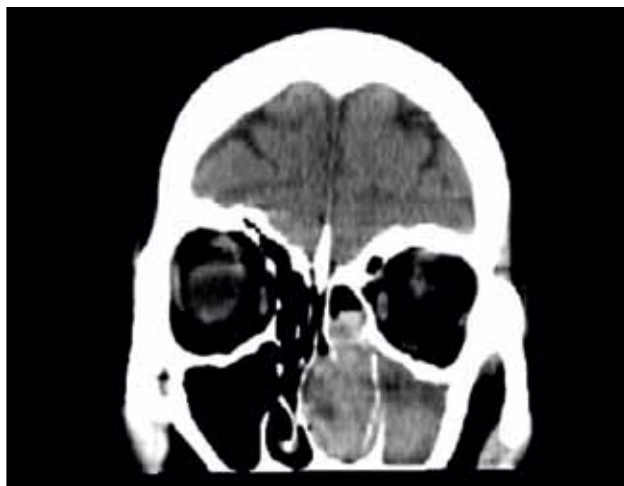


Figure 4 Cranio-facial CT scan, coronal and axial slices – voluminous tumour, 49/39/45mm, originating from the left postero-lateral nasopharyngeal wall, extended to the left maxillary sinus, nasal fossa, pterygoid fossa, left sphenoid sinus and left temporal fossa.

fossa – red, pulsatile tumor originating from the middle meatus, eroding the lateral nasal wall and covered with necrotic debris (Figure 3).

The cranio-facial CT-scan described a voluminous tumour measuring 49/39/45mm, originating from the left postero-lateral nasopharyngeal wall, extended to the left maxillary sinus, nasal fossa, pterygoid fossa, left sphenoid sinus and left temporal fossa, with muscular infiltration and fluid collection in all left sinuses (Figure 4).

The otomicroscopic examination revealed an air-fluid level in the left middle ear, the pure-tone audiometry and the tympanogram sustaining the conductive hearing loss and otitis media with effusion diagnostic.

The histopathologic examination of the tissue sample performed after biopsy established the final diagnosis - nasopharyngeal non-keratinizing cell carcinoma, the tumour's stage being IVA.

The particularity of the case was the time elapsed between the symptoms onset and diagnose -5 months.

Case 3

A 30 year-old woman presented to our clinic for bilateral neck masses, nasal obstruction and right ear blockage sensation. The otologic symptoms were the first ones appeared 21 months ago, followed by left adenopathy 3 months later. During the last 6 months the right cervical tumour mass started to be painful spontaneously and during palpation.

9 months before addressing to our Department the patient has been evaluated in another ENT Department where she was diagnosed with right otitis media and left adenopathy. She received antibiotic, NSAID and nasal decongestant.

Clinical examination revealed a neck mass in the IIB area (jugulodigastric lymph nodes) bilaterally – 4/3 cm, strong consistency, immobile on deep and superficial tissues, painful on palpation (Figure 5). The nasal endoscopic examination showed a voluminous tumour occupying the nasopharynx and block-

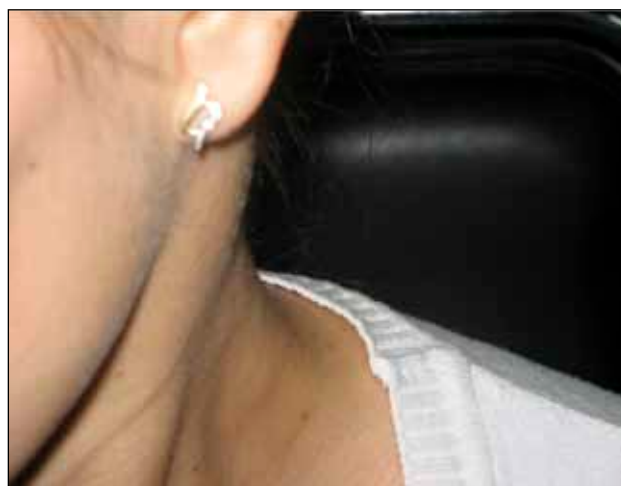


Figure 5 Bilateral cervical adenopathy a. right; b. left – IIB cervical nodes area (jugulodigastric lymph nodes)

ing both choanal openings (Figure 6).

Otoscopic evaluation showed air-fluid level and thickened tympanic membrane bilateral. The pure-tone audiometry and the tympanogram confirmed the bilateral serous otitis media clinic diagnostic.

Cranial CT scan described a tumour arising from the right postero-latero-superior nasopharyngeal wall, invading both Eustachian tubes, with retropterygoidian and perimandibular extension; fluid retention in both sphenoid sinuses (Figure 7).

In order to improve otologic symptoms a bilateral tympanostomy tube placement was performed.

Histopathologic result after taking biopsy fragments was poorly differentiated keratinizing squamous cell carcinoma. The tumor was in IVA stage.

In this case patient presented late for her symptoms



Figure 6 Nasal endoscopic examination - voluminous tumor blocking the left choanal arch



Figure 7 Cranio-facial CT scan, axial slices - nasopharyngeal tumour invading both Eustachian tubes.

and also the ENT specialist has not enough investigated patient condition.

Case 4

55-year-old male with recurrent episodes of left anterior epistaxis presented for left retroorbital pain and left palpebral ptosis with almost 2 weeks onset.

Clinical evaluation revealed left CN III and VI palsy - left palpebral ptosis, limitation of the left eyeball lateral movements and diplopia. Anterior rhinoscopy showed right anterior septum deviation, hypertrophy of inferior nasal turbinates and choanal openings blocked by a red tumour covered with mucous secretions and bloody streaks.

Cranio-facial MRI-scan described a nasopharyngeal tumour, 8.17/4.9/5.7 cm, extended to the left ethmoidal sinus, sphenoidal bone (sphenoid sinus, pituitary fossa, basilar apophysis) and to the odontoid base; flattened appearance of the pituitary gland (1.2/6.8/1.6cm); it was highlighted an angled trajectory of the internal carotid artery (Figure 8).

A biopsy was taken from the nasopharyngeal tumour, the histopathologic diagnosis being undifferentiated cell carcinoma.

DISCUSSIONS

Nasopharyngeal carcinoma is a tumor arising from the epithelial cells that cover the nasopharyngeal surface, usually originating from the lateral wall of the nasopharynx. Cervical lymph nodes metastases are typically for NPC, the distant once being described mostly in the bones, lungs, mediastinum and some in the liver⁷.

Nasopharyngeal carcinoma is widespread but occurs at high frequency in Southern China, Hong Kong, Tai-



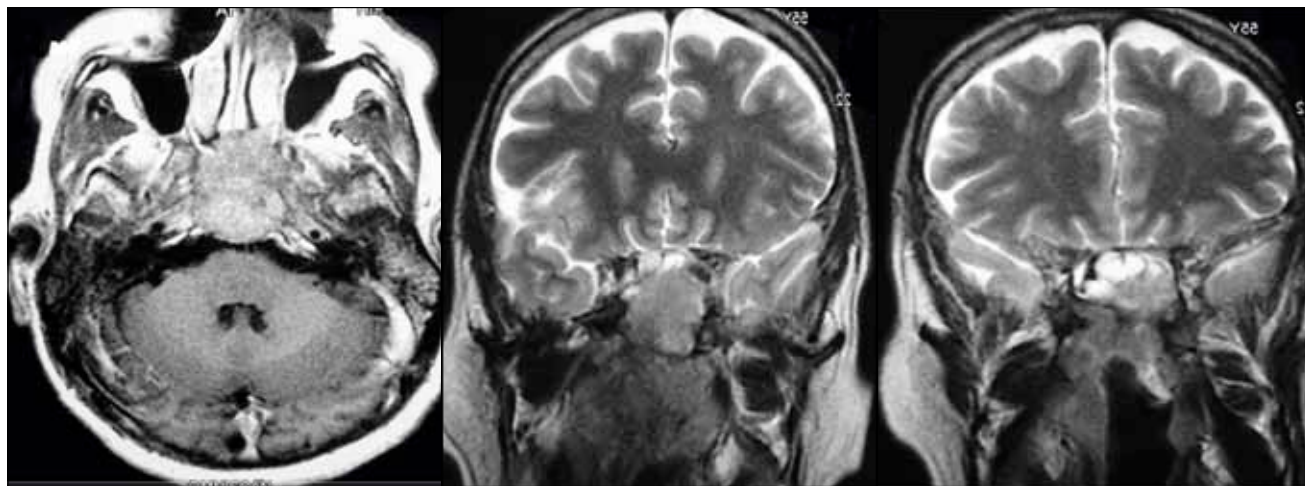


Figure 8 Cranio-facial MRI, axial and coronal slices - nasopharyngeal tumour extended to the left ethmoid sinus, sphenoid bone and to the odontoid base.

wan, Singapore and Malaysia^{8,9}. Its incidence varies from <1 in Europe and North America to 20-30/100000 in the countries before mentioned^{2,10}.

Men are twice or three times as likely to develop NPC as women and the incidence rate is higher between 20 and 50 years of age^{2,11,12}. In our study the ratio was 3.5:1.

Concerning the aetiology, many possible factors are described in the specialty literature, such as: Epstein-Barr virus infection (EBV), genetic susceptibility, exposure and consumption of food (in particular salted fish - containing carcinogenic volatile nitrosamines), etc.¹³. EBV is an oncogenic human gamma-herpes virus that infects more than 90% of the human population. There are studies that certify the fact that EBV genome is present in almost all NPC tissues¹⁴. It was found that the polymorphism of nitrosamine metabolizing genes, like CYP2A6 and CYP2F1, may play an important role in NPC susceptibility¹⁴.

Also, it was discovered that genomic instability or aggravation of genomic alterations could be early events markers in NPC evolution. To prove this hypothesis were used tree model to analyze comparative genomic hybridization, the results showing that the chromosome 12 is the one involved, especially consistent loss of 3p¹⁴.

High levels of epidermal growth factor and its receptor (EGFR) and vascular endothelial growth factor (VEGF) were found in patients with NPC and were correlated with malignant progression and poor prognostic².

Early exposure and consumption of salted fish diet were found to be important risk factors because it contains high levels of carcinogenic volatile nitrosamine (was showed the high incidence of NPC in "boat people")².

NPC is frequently misdiagnosed due to its anatomical position and the common symptoms that appear in disease's natural history. Frequently, first symptom is one of the following: nasal obstruction, hearing loss,

blocked ear sensation, otalgia, epistaxis, headache or cranial nerves palsies.

The World Health Organization classified nasopharyngeal carcinoma into three histopathologic groups¹⁵:

- type I: keratinizing squamous cell carcinoma
 1. well differentiated (G1)
 2. moderately differentiated (G2)
 3. poorly differentiated (G3)
- type II: nonkeratinizing cell carcinoma
- type III: lymphoepithelioma (Schmincke-Regaud tumour) – undifferentiated tumour

In a National Cancer Data Base study on 5069 patients diagnosed with NPC in USA between 1985 and 1989 was highlighted the importance of different types of nasopharyngeal malignant tumours. According to their results, the 5 years survival rate is 37% for type I, 65% for type II and 64% for type III, which means that the keratinizing squamous cell carcinoma has the poorest prognosis².

In early phase the tumor may grow without producing any signs or symptoms and patients may perceive them as not bothersome¹⁶. Most of the patients present with advanced stages of nasopharyngeal carcinoma – in our study almost 50% of the patients were diagnosed with NPC stage III and IV. In the international literature there are studies that relate a late diagnosis of the nasopharyngeal carcinoma¹⁶⁻¹⁸. El-Sherbieny et al. found that 86% of their patients were diagnosed in advanced stages – III and IV¹⁷.

In a study performed in Queen Elisabeth Hospital from Hong Kong between 1976 and 1985 the mean symptom duration was 8 months¹⁸. Later on, in 1998, Lee et al. reported a mean duration of 2.9 months between the first symptom onset and first medical appointment². Our results showed that, in Romania of the XXI century most patients with NPC wait between 6 and 12 months from the onset of the symptoms until presenting to a medical investigation.

In Romania, we consider that the late diagnose of

NPC can be due to misdiagnose, but also due to the poor medical education of the population. In the same time, poor quality of medical equipment and sometimes, superficiality with which the patient is treated, can be considered another two causes for advanced NPC diagnosis.

Concerning the therapeutic approach, radiotherapy, as a single-modality treatment, remains the standard treatment for NPC. The initial radiotherapy target has to include the nasopharynx, as well as both retropharyngeal, jugulodigastric, inferior cervical region, posterior chain and supraclavicular lymph nodes².

CONCLUSIONS

Nasopharyngeal carcinoma is a distinct type of head and neck cancer concerning epidemiology, pathology, clinical presentation and responses to treatment.

The extent of disease at diagnosis of NPC is the most important prognostic factor. In Romania over 50% of the patients with newly diagnosed NPC present with locally advanced disease - stage III or IV. A large proportion of the patients presents at least 6 months after the first symptom onset.

Due to its very wide spectrum of symptoms, a high degree of suspicion from the ENT specialist and an increased awareness of the patient are crucial for the recognition of an early lesion.

At last, but not the least, we consider that one of the most important steps in minimising the delay in the diagnosis and treatment of nasopharyngeal carcinoma is a greater concern effort to improve public health education and develop screening programs.

REFERENCES

- Low W.K.C., Rangabashyam M. - Ear-Related Issues in Patients with Nasopharyngeal Carcinoma. In: Chen S.S. editor - Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma. InTech, Croatia, 2012;p.155-173.
- Lee A.W.M., Ko W.M., Foo W., Choi P., Tung Y. - Nasopharyngeal carcinoma time lapse before diagnosis and treatment. HKMJ, 1998;4:132-6.
- Binder D.K., Sonne D.C., Aschbeln N.J. - Cranial Nerves: Anatomy, Pathology, Imaging. Thieme Medical Publishers, 2010;p.29-81.
- Cho S.H., Jin B.J., Lee Y.S., Paik S.S., Ko M.K., Yi H.J. - Orbital Apex Syndrome in a Patient with Sphenoid Fungal Balls. Otorhinolaryngology, 2009;2(1):52-54.
- Sarafoleanu C. ed. - Tratat de Chirurgie – Otorinolaringologie si Chirurgie Cervico-Faciala. 2nd Edition, 2012;p.256-262.
- Lee C.C., Huang T.T., Lee M.S., Hsiao S.H., Lin H.Y., Su Y.C., Hsu F.C., Hung S.K. - Clinical application of tumor volume in advanced nasopharyngeal carcinoma to predict outcome. Radiat Oncol., 2010;5:20.
- Sze W.M., Lee A.W., Yau T.K., Yeung R.M., Lau K.Y., Leung S.K., Hung A.W., Lee M.C., Chappell R., Chan K. - Primary tumor volume of nasopharyngeal carcinoma: prognostic significance for local control. Int J Radiat Oncol Biol Phys., 2004;59:21-7.
- Lee C.C., Huang T.T., Lee M.S. - Clinical application of tumor volume in advanced nasopharyngeal carcinoma to predict outcome. Radiation Oncology, 2010;5:20.
- Liu M.T., Hsieh C.Y., Chang T.H., Lin J.P., Huang C.C., Wang A.Y. - Prognostic factors affecting the outcome of nasopharyngeal carcinoma. Jpn J Clin Oncol., 2003;33:501-8.
- Labidi S., Aissi S., Zarraa S., Gritli S., Mrad M.B., Benna F., Bous-sen H. - Update on Medical Therapies of Nasopharyngeal Carcinoma. In: Chen S.S. editor - Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma. InTech, Croatia, 2012;p.179-184.
- Snow J.B. Jr, MD, Ballenger J.J. - Ballenger's Otorhinolaryngology Head and Neck Surgery. Sixteenth Edition. Hamilton, Ontario: DC Decker, 2002;p.1407-1417.
- Che C.T. - Nasopharynx. In: John H. - Scott-Brown's Otolaryngology vol.5, 6th Ed. London, Butterworth, 1997;13:4-30.
- Brennan B. - Nasopharyngeal carcinoma. Orphanet J Rare Dis., 2006;1:23.
- Cho W.C. - Nasopharyngeal carcinoma: Molecular biomarker discovery and progress. Molecular Cancer, 2007;6:1.
- Greene F.L., Page D.L., Fleming I.D., Fritz A.G., Balch C.M., Haller D.G., Morrow M. - AJCC Cancer Staging Manual 6th edition. New York: Springer - Verlag, 2002.
- Licitra L., Bernier J., Cvitkovic E., et al. - Cancer of the nasopharynx. Crit Rev Oncol Hematol., 2003;45:199-214.
- El-Sherbieny E., Rashwan H., Lubis S.H., Choi V.J. - Prognostic factors in patients with nasopharyngeal carcinoma treated in Hospital Kuala Lumpur. Asian Pacific J Cancer Prev, 2011;12:1739-1743.
- Lee A.W., Foo W., Law S.C., et al. - Nasopharyngeal carcinoma - presenting symptoms and duration before diagnosis. HKMJ, 1997;3:355-61.