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CLINICAL, HISTOPATHOLOGICAL AND THERAPEUTIC ASPECTS OF RARE LESIONS FROM EAR, NOSE AND THROAT REGION

– A B S T R A C T –

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GENERAL PART

II. CONCEPTUAL APPROACHES TO RARE SINONASAL PATHOLOGY

Fundamental knowledge of the **anatomy of the sinonasal region** is essential both for understanding the complex physiological mechanisms at this level and for the diagnosis and therapeutic approach to rare sinonasal pathology. The sinonasal region plays a role in humidifying, heating and filtering air, acting as a conduit for inspired air. It also has a role in protecting the respiratory tract through the use of the mucociliary system. The sinonasal mucosa also houses olfactory receptors responsible for receiving olfactory signals which are then sent to the cortex to be processed, integrated and converted into olfactory sensation.

The nasal cavity is lined by keratinized squamous stratified epithelium with numerous hair follicles, sebaceous and sweat glands, mainly located in the anterior portion. Posteriorly, the squamous epithelium is continued by respiratory-type epithelium lining both the posterior nasal cavity and the paranasal sinuses. The nasal mucosa is thicker and more vascularised at the turbinate and nasal septum.

Respiratory epithelium has three main cell types: basal cells, goblet cells and ciliated cells.

II.2. THE CURRENT LEVEL OF KNOWLEDGE IN THE FIELD OF RARE SINONASAL PATHOLOGIES

II.2.1. MUCOSAL SINONASAL MELANOMA

Mucosal sinonasal melanoma is a rare and highly aggressive tumour originating in melanocytes, cells of neuroectodermal origin, located in the sinonasal mucosa. It constitutes less than 1% of all melanomas and has an incidence of approximately 0.3 cases per million inhabitants per year.

Due to the fact that patients with synonadal melanoma frequently present at an advanced stage of disease, the mortality of this neoplasm is very high, with a median survival rate of approximately 30 months, and a low 5-year survival of 8-30%.

Compared to cutaneous melanomas, the pathogenesis of mucosal melanoma is poorly understood. Possible aetiological factors include chronic smoking, occupational exposure to toxic formaldehyde substances and human papilloma virus (HPV) infection.

On **clinical point of view**, the symptomatology of patients with mucosal sinonasal melanoma is nonspecific, presenting with signs of partial or complete nasal obstruction, frequently unilateral, accompanied by epixtasis and rhinorrhea, and in advanced stages by facial pain and marked weight loss. The tumour has a slowly progressive growth initially and then rapidly progressive intrasinus or intranasal growth. Most tumours originate from the septum or lateral walls of the nasal cavity. In advanced stages, a tumour mass protruding through the nasal fossae to the outside can be clinically detected.

On **microscopic examination**, in the usual staining, mucinous melanoma shows a solid, organoid, trabecular, alveolar or combined growth pattern and may present epithelioid cells, spindle cells, mixed celularity, small basaloid cells.

Poorly differentiated tumours require **immunohistochemical evaluation** for a definitive histopathological diagnosis with melanocytic markers.

Sinonasal melanoma with melanocytic pigment deposition requires **differential diagnosis** with other melanocytic lesions such as melanosis and melanocytic nevus.

Differential diagnostic problems are present in achromatic lesions or in poorly differentiated lesions with marked pleomorphism, which may mimic clinically, but also histopathologically an undifferentiated sinonasal carcinoma, sarcoma or lymphoma, and microscopically require immunohistochemical study to establish the cell lineage of origin. In these cases, immunohistochemical melanocytic markers.

II.2.2. OLFACTORY NEUROBLASTOMA

Olfactory neuroblastoma is a malignant tumour originating in the olfactory neuroepithelial cells of the sinonasal mucosa.

Clinically, olfactory neuroblastoma often has a subtle presentation mimicking inflammatory or infectious disease, which can lead to delayed diagnosis. Nasal obstruction and epistaxis are typical early manifestations, however, other more specific symptoms may occur depending on the location and extent of the tumor, such as anosmia and rhinorrhea, which may precede the diagnosis of olfactory neuroblastoma by several years.

Olfactory neuroblastoma belongs **microscopically** to the category of small, round, blue cell tumours, along with Ewing's sarcoma, small cell neuroendocrine carcinoma and lymphoma. This generic designation brings together tumors characterized on standard hematoxylin-eosin stained preparations by the presence of small, relatively monotonous cells with poorly quantitatively represented cytoplasm and rounded nuclei with finely granular chromatin. The **immunohistochemical profile** includes positivity for melanocytic markers.

Due to the morphological features identified in the usual staining, olfactory neuroblastoma requires **differential diagnosis** with the whole category of small and round cell tumours, namely small cell neuroendocrine carcinoma, Ewing's sarcoma, alveolar rhabdomyosarcoma, small cell mucous melanoma and lymphoblastic lymphoma.

II.2.3. EXTRASKELETAL EWING SARCOMA/PERIPHERAL NEUROECTODERMAL TUMOR (PNET)

Ewing's sarcoma with primary sinonasal location is an extremely rare tumour, with less than 100 cases reported in the literature to date. It affects children, adolescents and young adults in their 2nd and 3rd decade of life, with males being more prone to this pathology compared to females. Studies to date have not been able to identify possible environmental factors involved in the etiopathogenesis or a familial predisposition.

Clinically, the symptomatology is also nonspecific in this case; most patients with sinonasal Ewing's sarcoma present with a 5-10 cm diameter tumor formation, which causes nasal obstruction, rhinorrhea and epistaxis.

Microscopic examination in the usual staining reveals the presence of a small blue cell tumour proliferation with a solid and occasionally pseudoalveolar growth pattern, consisting of plaques and lobules of tumour cells. The tumour cells are small, uniform in size, with indistinct cell boundaries and quantitatively poorly represented cytoplasm, pale or pale-eosinophilic, with increased glycogen content. Intracytoplasmic glycogen is evident by histochemical PAS staining in magenta red. Tumour cell nuclei are monotonous, oval, with smooth outline and fine granular chromatin pattern, with small, punctiform, inconsistently observable nucleolus. Mitotic activity is usually low to moderate, with the presence of typical and atypical mitoses.

Tumor cells characteristically show **immunoreactivity** for CD99 (intense and diffuse membrane expression) and FLI-1 (cytoplasmic immunolabeling in about 90% of cases).

Differential diagnosis includes all small blue cell tumours: lymphoblastic lymphoma, poorly differentiated synovial sarcoma, alveolar rhabdomyosarcoma, olfactory neuroblastoma, small cell carcinoma and variant mucinous small cell melanoma.

II.2.4. PRIMARY SINONASAL NEUROENDOCRINE CARCINOMA

Primary sinonasal neuroendocrine carcinoma is an epithelial tumor with predominantly neuroendocrine differentiation, first described as an entity by Silva et al. in 1982. The nasal cavity and paranasal sinuses are an extremely rare location for neuroendocrine tumors compared to digestive and pulmonary sites and account for approximately 3% of all sinonasal tumors.

The **clinical presentation** of primary sinonasal neuroendocrine carcinoma is similar to that of other malignancies occurring in the sinonasal tract. Initial symptoms are non-specific, with the disease beginning with nasal obstruction, rhinorrhea, facial pressure, headache, hyposmia, epistaxis, and patients are often initially treated for benign inflammatory conditions, leading to delayed diagnosis.

Histologically, neuroendocrine carcinomas are classified according to the degree of cell differentiation into well, moderately and poorly differentiated. Poorly differentiated neuroendocrine tumours develop in the sinonasal tract. This category is subdivided according to cell morphology into small cell and large cell neuroendocrine carcinoma.

Cell morphology in standard staining classifies these tumours into the group of small, round cell tumours and requires diagnosis of certainty by **immunohistochemical study**. Thus tumour cells are diffusely and intensely positive to neuroendocrine makers: synaptophysin, chromogranin, neuron-specific enolase and CD56. Markers of epithelial origin are also positive.

Primary sinonasal neuroendocrine carcinoma necessitates first **differential diagnosis** with all tumours in the small round cell tumour category, namely olfactory neuroblastoma, Ewing's sarcoma, alveolar rhabdomyosarcoma, mucinous small cell melanoma and lymphoblastic lymphoma.

II.2.5. GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an idiopathic vasculitis of the middle and small arteries characterized by necrotizing granulomatous inflammation of the respiratory tract with coexisting glomerulonephritis. The estimated incidence of the disease in Europe is 5-10 cases per 1 million individuals in the general population. The disease affects patients of all ages, but the most common age of presentation is the 6th and 7th decade of life. In 80%-95% of patients, the first symptoms of granulomatosis with polyangiitis are otorhinolaryngological manifestations of the head and neck.

Most often, the **symptoms** of granulomatosis with polyangiitis belong to the classic triad: upper respiratory tract involvement, lung involvement and kidney involvement, although any organ may be involved. In some cases, the otorhinolaryngological symptoms are the only sign of the disease and constitute the limited form, in contrast to the more advanced stages which have associated systemic vasculitis and constitute the generalised form. The limited phenotype is often more recurrent and refractory and affects the younger female population. The generalised form usually includes renal and/or pulmonary involvement and systemic symptoms such as fever, asthenia, anorexia or weight loss are most common. During the course of the disease, it is possible to transform from the limited to the generalized form and vice versa.

Microscopic examination of biopsy specimens collected from the sinonasal region and establishing a histopathological diagnosis of granulomatosis with polyangiitis is often difficult in current practice. Microscopic appearances may be dominated by a marked acute or chronic inflammatory process, which may mask vascular structures with vasculitis lesions. Also, in the early stages of disease, granulomas may not be found on histological slides, making diagnosis difficult.

Necrotizing vasculitis lesions involve small caliber arterial and venous vascular structures, and there may be aspects of acute, granulomatous vasculitis or vasculitis in the fibrotic healing stage. Acute stage vasculitis lesions are characterized by fibrinoid necrosis of the vascular wall and its infiltration with neutrophilic granulocytes. The inflammatory and necrotic process may involve the entire circumference of the vascular lumen.

The presence of a marked inflammatory process associated with ulcerations of the lining mucosa requires the **differential diagnosis** of granulomatosis with polyangiitis with an infectious process and with sinonasal lymphoma. To exclude a specific infectious process, anatomo-clinical correlations and identification of a possible infectious agent by microbiological culture are necessary. In general, sinonasal infections are not associated with pulmonary or renal manifestations, nor with increased serum ANCA autoantibodies, as in granulomatosis with polyangiitis.

III. CURRENT DIAGNOSTIC AND THERAPEUTIC APPROACHES IN RARE SINONASAL PATHOLOGY

Patients with **mucosal sinonasal melanoma** benefit from personalised treatment determined within a multidisciplinary medical team. The mainstay of treatment, in the case of localised disease, with or without lymph node metastases present, is complete tumour resection with histologically negative margins. The choice of surgical technique depends on the localization of the primary tumour as well as its capacity for local invasion. The postoperative benefit of radiotherapy is unclear, and it is used either palliatively or adjuvantly for local disease control. Chemotherapy is reserved for cases with advanced disease or metastatic disease, with a palliative role and limited impact on survival. Immunotherapy in combination with chemotherapy has been used in the treatment of isolated cases of mucosal melanoma, but the efficacy of this combination should be evaluated in much larger groups. The emergence of cytogenetic techniques opens new therapeutic opportunities for the future.

Treatment of **olfactory neuroblastoma** consists of endoscopic surgical resection of the tumour combined with radio- and chemotherapy. Endoscopic endonasal surgery is most commonly recommended and used, due to effective local control as well as a low morbidity rate.

Surgical treatment is complemented with radiotherapy sessions to reduce brain and eye toxicity over time, as well as neoadjuvant chemotherapy, which can improve surgical management by reducing tumor size and complications.

The occurrence of local recurrences at a long-time distance from the initial tumour requires surveillance of patients with olfactory neuroblastoma over a long period of time. It is also recommended to include PET-CT in the follow-up protocol of patients with olfactory neuroblastoma because of the risk of distant metastases.

There are some past studies recommending the use of radiotherapy treatments for patients with **Ewing sarcoma**, especially for cases with suboptimal resection, but to date there is not enough evidence known to improve survival rates when using adjuvant radiotherapy.

Current studies report the value of chemotherapy and surgical intervention as first-line treatment and postoperative radiotherapy only for tumours larger than 10 cm. Periodic follow-up of patients with Ewing sarcoma is also required, at 3 months in the first year after diagnosis, then at 6 months in the second year and annually thereafter. All cases of Ewing sarcoma are discussed in a multidisciplinary oncology committee, and the follow-up plan can be individualized according to the aggressiveness of the tumor and the status of the patient.

As there is no specific recommendation on the management of **neuroendocrine tumours**, treatment options are extrapolated from pulmonary counterpart. Traditionally, the treatment of sinonasal neuroendocrine tumours is surgical resection followed by radiotherapy and then chemotherapy for resectable tumours, and concomitant radio- and chemotherapy for unresectable tumours. Fitzek and collaborators reported good results in a series of patients treated with two initial cycles of cisplatin and etoposide. In addition, patients responsive to photon/proton radiotherapy also received two cycles of etoposide and cisplatin, while unresponsive patients underwent only surgical resection followed by postoperative photon/proton radiation. When cervical lymph nodes are positive, neck dissection is indicated and given the retropharyngeal and parapharyngeal lymphatic drainage system radiation to this area is indicated.

In terms of treatment of **granulomatosis with polyangiitis**, glucocorticoids combined with cyclophosphamide have been shown to achieve remission in most patients. Some studies also report achieving complete remission after the use of methotrexate and glucocorticoids in combination. One randomised trial supported the benefits of cyclosporine after remission induction. The literature shows some success in inducing remission with the use of immunosuppressive agents such as rituximab, infliximab and 15-deoxyspergualin.

SPECIAL PART

V. RARE SINONASAL PATHOLOGIES DIAGNOSED IN THE WESTERN PART OF THE COUNTRY

V.1. STUDY GROUP, INCLUSION AND EXCLUSION CRITERIA

The study is a retrospective one, with chronological extension over a period of 7 years, respectively January 2016 - December 2022 and includes rare pathologies developed in the sinonasal region and diagnosed in the Pathology I Service of the Timișoara Emergency Hospital. All biopsy specimens are collected in the Otorhinolaryngology Clinic of the same hospital during the specified period. The cases are identified using the specimen reception records from the Pathology Service and are integrated into the clinical context using the SCMUT computer database.

V.3. RESULTS

V.3.1. MUCOSAL SINONASAL MELANOMA

Nine cases of primary mucosal sinonasal melanoma were included in the study.

All patients in the selected group are in the 5th-7th decade of life, with a mean age at diagnosis of 67.77. The incidence between genders is approximately equal, with a slightly increased proportion for male sex, 55.55% (5 patients), compared to female sex, 44.45% (4 patients). Of these, the majority are smokers, 77.77% (7 patients), and one reports occasional alcohol consumption (case 6).

An analysis of the topography of the lesions shows that the majority of syn-nasal melanomas develop unilaterally (88.88), in the right or left nasal fossa, 4 cases each (44.44% for each nasal fossa). Only one case, shows bilateral localization of the lesion, also accompanied by involvement of the right sphenoid sinus, frontal sinus and orbit.

Histopathological examination of the biopsy specimens shows that all mucosal sinonasal melanomas have the same cellular subtype, respectively all are melanomas with epithelioid cells. The presence of melanin pigment was found in 6 cases (66.66%), they have minimal, moderate or marked amount of melanin arranged intracytoplasmically, while 3 cases (33.4%) are mucosal melanomas. All tumors show increased mitotic activity, with a mitotic index above 5%, with an average of 12 mitoses/10 microscopic fields at 40x objective.

Immunohistochemical profiling was required in 5 cases. The other 4 cases did not require immunohistochemical rections due to the presence of melanic pigment.

From the selected lot we present two particular cases, namely case 6 and case 7.

Case 6 is a 58-year-old female patient presenting with unilateral right nasal obstruction, with a history of about six months, with multiple episodes of bilateral epistaxis, reason for which admission is decided. From the patient's history we learn that she is on antihypertensive treatment and has a hereditary history of heart disease. Affirmatively, the patient does not smoke and consumes alcohol occasionally.

Anterior rhinoscopy reveals a vegetative tumour mass in the right nasal fossa with a smooth, painless surface that bleeds spontaneously and on palpation. Under general anaesthesia the tumour is excised and the specimen is sent to the Pathology Department.

On the basis of morphological features in hematoxylin-eosin staining and immunohistochemical profile, the diagnosis of mucosal nasal melanoma with epithelioid cells is made. The patient is referred to the oncology service but refuses oncological treatment.

Two years after surgery, in March 2019, she presents with a bleeding tumor mass occupying the posterior and middle third of the right nasal fossa, with infiltration of the upper third of the nasal septum. Microscopic examination confirms tumor recurrence.

Case 7 is a 66-year-old male patient presenting to the ENT Department of the Timisoara Municipal Emergency Hospital with a recurrence of nasal mucosal melanoma tumour approximately one year after surgery performed in a specialized department in Cluj. The patient presented with a bleeding nasal-orbital-sphenoidal tumour mass covered with mucopurulent secretions, associated with submandibular adenopathy. Resection of the tumor

among with the eyeball, excision of the right frontal and sphenoidal sinus mucosa, suborbital fat and removal of the right submandibular lodge and posterior jugal ganglionic chain are performed. No major complications are present after surgery.

Microscopic examination confirmed the diagnosis of recurrent nasal mucosal melanoma with epithelioid cells. The tumour invades the nasal mucosa, sphenoid sinus, frontal sinus, periorbital fat and the internal and external angle of the eyeball, without invasion of the eyeball and without lymph node metastases. Surgical excision was performed within indemn tissue. The patient is currently under oncological follow-up.

V.3.2. OLFACTORY NEUROBLASTOMA

A 45-year-old male patient was admitted to the ENT department with unilateral epistaxis in the right nasal cavity. He initially received conservative treatment with Merocel, anterior nasal buffer, but in a few days, he returned with recurrent symptomatology. Endoscopic examination revealed a single, smooth, tumour mass located in the right nasal fossa.

Head and neck CT is performed. CT examination identifies a heterogeneous, natively hyperdense tissue mass filling the entire right nasal cavity with bony erosion and remodeling and partial visualization of the right inferior turbinate processes. The native CT appearance is not suggestive of lesional framing, with inverted papilloma, sinonasal polyp, and adenocarcinoma entering the discussion. The right maxillary sinus shows increased tissue density and fluid content.

Subsequently, abdominal and thoracic CT and MRI examinations are also performed, with no evidence of distant metastases. The patient was classified according to the Kadis staging system, the tumour being located in the nasal fossa, without intracranial extension or erosion of the cribriform plate.

Endoscopic surgery is decided, with tumor excision with negative margins, right maxillary antrostomy and Merocel tampon application for 48 hours. In order to avoid postoperative infections, prophylactic antibiotic therapy is used for 72 hours, starting on the day of surgery. No major complications are identified and the patient is discharged less than 7 days postoperatively.

After endoscopic surgical removal of the tumour and confirmation of the diagnosis by pathological examination, the patient is referred for radiotherapy, undergoes 33 radiotherapy sessions (DT = 50 Gy/fr/38 days) in the right nasal fossa. Radiotherapy was well tolerated.

Patient monitoring is carried out in the oncology and radiotherapy departments, through postoperative imaging examination of the head and neck. No tumour recurrences are identified. ENT monitoring is scheduled every 3 months in the first postoperative year with nasal endoscopy, then every 6 months in the second and third year and annually thereafter, with no specific relapse or symptoms identified.

In the fifth year after the initial diagnosis, the patient has lumbosacral and humeral bone pain. CT and MRI examination shows multiple osteolytic lesions disseminated in the C6, C7, C8, T7 and T11 vertebral bodies (up to 16 mm in size), as well as in the costal arches and pelvis, 11 cm in size, located in the right iliac wing, extending into the right iliac muscle, and a 10 mm lesion in the left iliac wing. CT scan of the head and neck identifies marked circumferential thickening of the right maxillary sinus mucosa and normally aerated paranasal sinuses. Imagistically identified bony lesions raise the suspicion of multiple myeloma, with distant dissemination of olfactory neuroblastoma from the patient's history also coming into question.

Incisional biopsy of the mucosa of the maxillary sinus is performed under local anaesthesia, then the patient is referred for haematological consultation and scheduled for positron emission computed tomography (PET-CT) and bone biopsy.

Biopsy of the sinus mucosa shows thickening of the overlying epithelium and edema in the lamina propria, associated with diffuse chronic inflammatory infiltrate and absence of tumor cells.

PET-CT reveals activated metabolism of a tumour mass located in the right iliac wing, 10/7.5 cm in size, invading neighbouring endo- and exopelvic structures. The tumour tissue

shows inhomogeneous FDG uptake. Other FDG-capturing osteolytic lesions, having invasive and dimensional progression compared to the CT scan performed one week earlier

Bone marrow biopsy reveals a medullary iron blockage with moderate plasma cell hyperplasia and 4.5% of nucleated cell elements affected. The diagnosis of monoclonal gammopathy of unspecified aetiology, IgG lambda chain type, is established on the basis of total blood cell count, associated with protein electrophoresis, serum electrophoresis, immunocantification and bone marrow biopsy data.

Subsequently, a bone biopsy is taken from the iliac lesion, confirming the diagnosis of IgG multiple myeloma with kappa chains, based on the immunohistochemical profile.

The disease is classified as stage III according to the International Staging System (R2-ISS) for overall survival of multiple myeloma. The patient has hematologic treatment with daratumumab, bortezomib, thalidomide, dexamethasone and bisphosphonate, with bone pain improvement. The patient is currently in the follow-up stage.

V.3.3. EWING'S SARCOMA

A 21-year-old male patient presents to the ENT Clinic in 2009 with unilateral nasal obstruction and repeated episodes of epistaxis. A nasal endoscopy revealed a vascularized tumor mass located in the left nasal fossa at the lateral wall. Under local anaesthesia a biopsy fragment is taken and examined microscopically.

On the basis of the histopathological examination and immunohistochemical profile, the diagnosis of sinonasal type hemangiopericytoma is established and follow-up is recommended.

Approximately 7 years after the initial diagnosis, the patient presents with left-sided nasal obstruction with oral breathing, purulent rhinorrhea and headache. Rhinoscopy reveals a highly vascularised tumour formation completely obstructing the left nasal fossa. Surgery under general anaesthesia was decided and a medial maxillectomy was performed.

Microscopic examination in the usual staining reveals in the left maxillary sinus and left nasal wall, a tumor proliferation with morphology classified as small, round tumors. Immunohistochemical investigations performed indicate positive, high intensity reaction for markers consistent with Ewingţs sarcoma.

V.3.4. SINONASAL NEUROENDOCRINE CARCINOMA

In 2023, an 87-year-old female patient presents to the ENT Clinic with left nasal obstruction and repeated episodes of rhinorrhoea over the past six months. Anterior rhinoscopy and nasal endoscopy are performed and a pseudotumoural formation is identified, located in the left nasal fossa, with extension towards the left maxillary sinus, bleeding on palpation with a buttoned stylus.

Excisional biopsy of the tumor formation, left ethmoidectomy and left nasal swab are performed. Intra- and postoperative evolution is favourable. Histopathological features in the usual staining correlated with the immunohistochemical profile incline the diagnosis towards a primary sinonasal neuroendocrine carcinoma.

V.3.5. GRANULOMATOSIS WITH POLYANGIITIS

The group selected for the study includes two patients with granulomatosis with polyangiitis. The first case is a 64-year-old male patient admitted to the ENT Clinic with the following symptoms: marked swelling of the nasal pyramid, diffuse midfacial and intense cranial pain, chronic bilateral nasal obstruction, muco-purulent rhinorrhea and repeated episodes of epistaxis.

Clinical examination reveals signs of acute inflammation, respectively swelling of the sinonasal and midfacial area, thickened, hyperemic, painful tegument spontaneously on palpation. No laterocervical adenopathy is identified on palpation.

Nasal endoscopy reveals the presence of an ulceration on the right lateral aspect of the nasal septum, microulcerations of the inferior nasal turbinate, bilateral, muco-purulent greenish-yellow crusts adherent to the nasal mucosa, which on detachment leave a bleeding area and free cavum.

The histopathological result, associated with the biological and immunological analyses, as well as the data provided by the rheumatological and nephrological examinations, support the diagnosis of granulomatosis with systemic polyangiitis with positive ANCA antibodies. The patient underwent specific treatment with antibiotics and corticosteroids and is currently under nephrological and ENT monitoring.

The **second case of granulomatosis with polyangiitis** is a 43-year-old female patient. The medical history reveals a variety of conditions.

Given the damage to the kidneys by chronic glomerulonephritis lesions, the patient is treated in the nephrology department with multimodal therapy, respectively corticotherapy (prednisone) and antibiotic therapy (cyclophosphamide). The renal disease is in remission under specific treatment.

Nasal endoscopy reveals the absence of septal cartilage, with the formation of a unicameral nasal cavity, with atrophic mucosa, bleeding on manipulation, covered with crusts. Associated with this is the marked diminution of the inferior and middle nasal turbinate and the presence of greyish-murky crusts in the nasopharynx.

V.4. DISCUSSIONS

The detection and diagnosis of rare tumours of the sinonasal tract is a challenge, requiring a multidisciplinary team of ENT clinician, radioimaging specialist and pathologist to assess the different manifestations of the disease, from clinical symptoms to imaging aspects and cell morphology.

Mucosal sinonasal melanoma is a distinct entity from cutaneous melanoma, having a different etiology, incidence, prognosis and treatment. In our country, its incidence is continuously increasing, due to genetic predisposition, but also due to lack of prevention.

Primary melanoma of the sinonasal mucosa is a rare tumour whose etiopathogenesis is not fully known. It is prognostically associated with a high recurrence rate and a high risk of metastasis, the 5-year overall survival rate does not exceed 40%. The median age of presentation for sinonasal mucosal melanoma is 65 years, affecting slightly more men than women, with a 3:2 sex ratio. No risk factors have been identified, although smoking and occupational exposure to formaldehyde have been suggested as risk factors for malignant transformation. A connection with human papillomavirus and herpesvirus has also been suggested but could not be confirmed.

Clinically, the most common location is the lateral nasal wall and nasal septum, but mucosal melanoma may also involve the paranasal sinuses with predominance on the maxillary sinus followed by the ethmoid, frontal and sphenoid sinuses. Patients present with non-specific symptoms, namely nasal obstruction, facial pain, epiphora, epistaxis and in advanced cases, facial deformities and locoregional adenopathy.

Nasal endoscopy allows topographic evaluation of the tumour, assessment of its size and appearance, as well as an assessment of tumour extension. In some cases, due to the marked tumour extension, it is difficult to determine the exact starting point.

Histologically, sinonasal mucosal melanomas are difficult to diagnose and have a worse prognosis compared to pigmented lesions, regardless of cell subtype. Approximately 40% of mucosal melanomas lack melanocytic pigmentation. Lack of melanocytic pigment and high histological grade challenge differential diagnosis and require immunohistochemical study. For these cases, positivity for melanocytic markers, associated with negative immunoreactivity for epithelial and mesenchymal markers, transgresses the diagnosis.

Approximately 50% of patients have local recurrence due to vascular invasion, the rich lymphatic network at this level and the multifocal nature of the lesions, and the overall prognosis is extremely poor. Monolidis & Donald reported in a study of 962 patients, a median survival rate at three years of 39.2% and at five years of 17.1%. In the literature, liver, lung, bone and brain metastases are seen in approximately 50% of cases, while lymph node metastases are found in approximately 20-40% of patients. If the metastasis is single and completely excised, the survival rate is prolonged.

The treatment of mucosal sinonasal melanoma is personalised and is determined by a multidisciplinary team including the oncologist. The mainstay of treatment for localised disease

with or without lymph node metastases is complete resection of the tumour with histologically negative margins. The choice of surgical technique depends on the location of the tumour and its extent. Despite surgical treatment, local recurrences are very common.

Literature data show that the postoperative benefit of radiotherapy remains unclear. It is used either palliatively or adjuvantly for local disease control. Chemotherapy is reserved as palliative treatment for advanced cases with metastatic disease, with limited impact on survival.

Studies in recent decades show the efficacy of using immunotherapy in combination with chemotherapy in the treatment of isolated cases of sinonasal mucosal melanoma, but the effectiveness of this combination should be evaluated in larger groups of patients. The emergence of cytogenetic techniques opens new therapeutic opportunities for the future.

Another rare tumour of the sinonasal region is the **olfactory neuroblastoma**, first described in the literature in 1924 and with a currently unknown etiopathogenesis. With a symptomatology dominated by nonspecific signs, the gold standard of diagnosis remains biopsy, followed by microscopic examination.

Morphologically classified in the broad category of small round cell tumours, the diagnosis of certainty is based on positive immunohistochemical reactions for S100 protein, Bcl2, PGP9.5 and markers of neuroendocrine origin, in combination with negative immunoreactions for markers of epithelial, muscle, melanocytic and lymphoid origin.

Based on our experience, we believe that the endonasal approach achieves a complete resection for small, localized lesions when reconstruction is not required, provided the resection has negative margins. Since at the time of diagnosis, the patient was at stage cN0M0, it was decided that a neck dissection was not necessary. Also, endonasal excision allowed rapid recovery and return to daily activities, improving quality of life.

The lack of experience, due naturally to the extremely low frequency of this pathology, prevents the possibility of classifying prognostic factors and carrying out specific treatment protocols. Several staging systems have been proposed. The most widely used is the one proposed by Kadish in 1976 and modified in 1993. Currently, the TNM staging system developed by the AJCC based on Dulguerov's modified version is applied.

The classic recommended treatment for olfactory neuroblastoma is endoscopic surgical resection combined with radio- and chemotherapy. Endoscopic endonasal surgery is preferable because of effective local control and low morbidity. In our center, we consider and use the open approach when there is extensive tumor with intracranial involvement or when a pericranial flap is needed for reconstruction.

Surgical treatment is complemented by newer radiotherapy techniques designed to reduce brain and eye toxicity over time. Neoadjuvant chemotherapy can improve surgical management by reducing tumour size and complications.

Neuroendocrine carcinoma is an extremely rare tumour located in the sinonasal cavity and the degree of differentiation is the main prognostic factor. Thus, well and moderately differentiated neuroendocrine carcinomas have lower distant metastasis rates and better survival (disease-specific survival at 5 years of about 70%) compared to poorly differentiated neuroendocrine carcinomas (about 40%). The latter are aggressive, fast-growing tumours with an increased tendency for local recurrence and distant dissemination. Also, immunohistochemically, poorly differentiated tumours may lose expression for neuroendocrine markers. Differential diagnosis with other poorly differentiated tumours with primary sinonasal localization, as well as differential diagnosis with metastases, is difficult but essential in subsequent therapeutic management. Therefore, histopathological diagnosis of certainty and immunohistochemical evaluation of these tumours requires the use of an extensive panel of immunohistochemical markers.

The limited number of cases published to date, as well as the difficulties in developing a diagnosis of certainty in a timely manner, hinder the assessment of the ideal treatment strategy and present a medical challenge for the multidisciplinary team. The unfavourable prognostic factor is the presence of locoregional extension, most commonly in the orbital region and the bones of the cranial cavity. Surgery followed by adjuvant radiotherapy has been the main approach for treating small cell tumours in the past decades, as Perez-Ordonez and co-workers show in their studies. Subsequently, neoadjuvant chemotherapy treatment followed

by radiotherapy courses showed good results, in studies reported by Fitzek and Bhattacharyya. Such a treatment protocol was also proposed for voluminous, surgically unresectable tumours by Babin, who showed a complete response to neoadjuvant chemotherapy correlated with improved survival at three years. In patients with advanced tumours, combined adjuvant radiochemotherapy also shows favourable results in resolving paraneoplastic symptoms such as inadequate antidiuretic hormone secretion syndrome, as shown by Vasan.

Granulomatosis with polyangiitis is a rare systemic disease whose etiology remains unknown. It is characterized microscopically by granulomatous vasculitis lesions present in small and medium-sized vessels, any organ can be affected, but most often the upper respiratory tract and the kidneys, the most common renal involvement being rapidly progressive necrotizing glomerulonephritis. All patients with granulomatosis with polyangiitis have cytoplasmic anti-neutrophil cytoplasmic antibodies.

Prompt diagnosis and early treatment can reduce morbidity and mortality. Up to 85% of patients present with respiratory tract involvement as the first sign of the disease, but a variety of manifestations may be encountered.

VI. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

VI.1. CONCLUSIONS

- Sinonasal mucous melanoma, olfactory neuroblastoma, extraskeletal Ewing's sarcoma, primary sinonasal neuroendocrine carcinoma and granulomatosis with polyangiitis are a group of very rare lesions found in the sinonasal region in current practice.
- In usual staining, mucous melanoma mimics any growth pattern, resembling a poorly differentiated tumour, especially in cases of acrome tumours such as carcinoma, sarcoma or lymphoma, while olfactory neuroblastoma and Ewing's sarcoma have microscopic features that classify them as small round cell tumours.
- Granulomatosis with polyangiitis can microscopically simulate an infectious inflammatory process, delaying diagnosis and therefore treatment, and therefore histochemical and immunohistochemical study is essential.
- Mucosal sinonasal melanoma is positive for melanocytic markers and the complete immunohistochemical profile consists of S100 protein, HMB45, Melan A\MART-1, MITF, tyrosinase and SOX10.
- The immunohistochemical profile of olfactory neuroblastoma includes diffuse cytoplasmic reaction for neuron-specific enolase, synaptophysin, chromogranin A, CD56 (NCAM) and beta-tubulin as well as variable S100 protein reactivity.
- Ewing sarcoma characteristically shows immunoreactivity for CD99 (intense and diffuse membrane expression) and FLI-1 (cytoplasmic immunolabeling), as well as focal expression for epithelial markers, respectively pancytokeratin AE1\AE3, but also for neuroendocrine markers: neuron-specific enolase, S100 protein, chromogranin, synaptophysin, CD56 and PGP9.5.
- Granulomatosis with polyangiitis requires evidence of inflammatory infiltrate with CD2, CD3, CD20 and CD56 as well as the affected vascular wall with CD31, CD34 and histochemical staining with argentic staining.

VI.2. PERSONAL CONTRIBUTIONS

The current PhD thesis aimed to identify and present the rarest primary lesions occurring in the sinonasal sphere. Following microscopic analysis in standard staining, it was observed that the lesions included in the study present morphological aspects overlapping a wide range of pathologies and require for differential diagnosis and histopathological diagnosis of certainty, the use of immunohistochemical reactions. The main problems of differential diagnosis in the rare sinonasal pathology are shown in Table 6.

The immunohistochemical study is limited in the pathology laboratory due to the high financial costs and due to a possible shortage of biospecific material. Thus, we have naturally found it necessary to develop an algorithm for morphological and immunohistochemical evaluation of rare lesions of the sinonasal region. This algorithm is schematically represented in Table 7.

VI.3. GENERAL CONCLUSIONS

- Lesions with primary sinonasal location present a diagnostic challenge for both the clinician and the pathologist.
- Due to the anatomical configuration, the sinonasal region is hardly accessible to the patient's eye and difficult to approach surgically, which explains a delay in the diagnosis of lesions at this level.
- The four tumour lesions are highly aggressive, have a high recurrence rate and are frequently diagnosed in advanced stages, and granulomatosis with polyangiitis is an autoimmune disease that rapidly progresses to renal failure and death.
- For accurate histopathological diagnosis of rare sinonasal tumours, morphological aspects in the usual haematoxylin-eosin staining should be complemented by immunohistochemical reactions using a very extensive panel of antibodies.