sciendo

DOI: 10.2478/rjr-2025-0011

Romanian Journal of Rhinology, Volume 15, No. 58, April - June 2025

LITERATURE REVIEW

Sinonasal inverted papilloma: From etiology to treatment

Luciana Arjoca[1], Sebastian-Ionut Arjoca[1], Lucian Lapusneanu[2], Daniela Mihalache[3]

[1]"George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Targu Mures, Romania

[2]ENT Department, Braila County Emergency Clinical Hospital, Braila, Romania

[3]Department of Anatomopathology, Braila County Emergency Clinical Hospital, Braila, Romania

ABSTRACT

Inverted papilloma is a benign tumor that can become malignant. It most commonly develops on the lateral rhinosinusal wall and has a maximum incidence in the ethmoid cells. In most cases, it occurs unilaterally, the main symptom being nasal obstruction. Treatment can generally be performed through endoscopic sinus surgery, involving total resection due to its malignancy potential and risk of recurrence. Given the increased interest in this pathology, we present the most important aspects of sinonasal inverted papilloma, from etiology to therapeutic management, exemplifying with a case from our own experience.

KEYWORDS: inverted papilloma, nasal obstruction, HPV genotyping, ethmoidal cells.

INTRODUCTION

Inverted papillomas are rare benign tumors that develop from the Schneiderian respiratory membrane of the nasal cavity and paranasal sinuses. It was first described by Ward in 1854. In 1938, Rigertz identified the tendency for the tumor to grow and develop inward, proliferating into adjacent tissues. It has an extensive and locally invasive nature, with the possibility of intracranial invasion, a marked tendency for local erosion and tissue and bone destruction, frequent postoperative local recurrences, and the possibility of malignant transformation, often associated with squamous cell carcinoma[1].

Inverted papilloma accounts for 0.5-4% of all rhinosinusal tumors, with an incidence of 0.2-1.5 per 100,000 people. It is most commonly diagnosed in males, 4-5 times more frequently than in females, in the 5th to 7th decades of life. It can very rarely develop in children and young adults. In most cases, it develops unilaterally, originating on the lateral wall of the nasal cavity, at the middle meatus or at the ethmoidal level. Less frequently, the origin has been described in the frontal and sphenoid sinuses, the nasal septum, the nasal vestibule, the nasopharynx, or even the lacrimal sac[2].

The most common symptom associated with the presence of inverted papilloma is unilateral nasal obstruction, sometimes accompanied by repeated episodes of mild epistaxis[1,2].

EPIDEMIOLOGY – ETIOLOGY

In 2005, the World Health Organization classified Schneiderian papillomas into three categories: 1). inverted papillomas, which are characterized by an endophytic growth pattern and develop almost exclusively on the lateral nasal wall, in the maxillary antrum or in the ethmoid sinus, representing 70% of all sinonasal papillomas; 2). oncocytic or columnar (cylindrical) papillomas – these have the lowest incidence, representing 3-5% of all rhinosinusal papillomas (they occur in older patients compared to the other two categories and can develop both on the nasal septum and the lateral nasal wall); 3). exophytic or fungiform papillomas, which are characterized by an exophytic growth pattern and predominantly develop from

Corresponding author: Lapusneanu Lucian, MD, ENT Department, Braila County Emergency Clinical Hospital, 2 Buzau Street, Braila, Romania
ORCID: https://orcid.org/0000-0002-3817-4837
e-mail: llapusneanu@gmail.com
Received for publication: March 12, 2025 / **Accepted:** April 4, 2025

the nasal septum, at the junction between the cylindrical-ciliated respiratory mucosa and the squamous epithelium. Of the three types, the most frequently encountered is inverted papilloma with an incidence of 62%, followed by exophytic papillomas with a frequency of 32%, and cylindrical papillomas described in only 6% of cases[3].

The exact etiology of sinonasal inverted papilloma is not fully known. Several associated risk factors are mentioned in the literature, including: tobacco consumption, infections with human papillomavirus (HPV) or Epstein-Barr virus, prolonged exposure to air pollutants or irritating chemicals at the workplace (such as sawdust, nickel, flour or chromium), chronic inflammation of the rhinosinusal mucosa, allergic reactions and the development of nasal polyps[2,4,5].

Hyams et al.[6] found no evidence of a link between the occurrence of inverted papilloma, chronic inflammation and allergy. In another study, Phillips et al.[7] did not highlight a correlation between occupational history and the etiology of the papilloma. The direct etiological link between occupational exposure to various substances and the development of sinonasal inverted papilloma (IP) remains controversial. D'Errico et al.[8], in a questionnaire-based study, showed that among the 127 subjects evaluated, exposure to organic solvents was significantly associated with the occurrence of IP compared to exposure to welding fumes (OR 2.11 and OR 2.14, respectively). A statistically significant association was also reported by Sham et al.[9] in a study conducted on 50 patients with IP and 150 healthy individuals. On the other hand, Barberi et al.[10] reported that only 5% of the 70 patients diagnosed with IP included in their study had direct exposure to wood or leather dusts.

The involvement of smoking in the development of sinonasal IP is increasingly being evaluated, given that a higher incidence of recurrences and malignant transformation of inverted papillomas has been observed among smokers[1,11,12]. Regarding the risk of recurrence, Li et al.[12] reported that among 53 patients with SNIP, treated at Zhengzhou University Hospital between 2019-2023, smoking (OR = 10.08, 95% CI = 1.32-77.15) was an important and significant risk factor compared to allergies, alcohol consumption, along with a history of previous surgery (OR = 17.26, 95% CI = 2.69-110.76). Dictor et al.[11] investigated the association between IP and non-sinonasal head-and-neck carcinoma (197 patients with IP and 15,983 with nasal polyps) showing an incidence of 12.8 (95% CI, 3. 7 to 50; $p < 0.0001$) for non-sinonasal head-and-neck carcinoma, with a recurrence rate of IP in smokers of 28.2% versus 10.7% in non-smokers. In a study conducted on 162 patients diagnosed with sinonasal IP, Hong et al.[1] showed that smoking may be statistically significantly associated with malignant transformation of IP. 26.4% of the smoking patients included in the study (n=53) were diagnosed with squamous cell carcinoma and only 2.8% of the non-smokers (n=109) showed malignant transformation (OR=12.7; $p<0.001$).

Several studies demonstrate that various viruses are involved in the etiology of inverted papilloma, the most frequently implicated virus being the human papillomavirus (HPV)[4,5,13]. Studies and meta-analyses assessing the role of HPV in the pathogenesis of inverted papilloma have reported a prevalence ranging between 17% and 38%, with a higher frequency of HPV association in IP with severe dysplasia or malignant transformation, compared to IP without dysplasia or with mild dysplasia (55% versus 22%, $p < 0.02$)[14-16]. HPV has been detected in approximately 37% of sinonasal inverted papillomas, suggesting a possible involvement in the pathogenesis of these lesions. Subtypes 6 and 11 are associated with benign papillomatous lesions, while strains 16 and 18 are considered oncogenic and are associated with malignant transformation[17,18]. In a 2017 study conducted on 80 sinonasal IP biopsy samples, Liu et al.[19] detected 47 HPV-positive samples (58.8%) through HPV genotyping (PCR for HPV-DNA), with HPV11 being the most frequently identified subtype (20/53, 37.7%). In 2020, Frasson et al.[20] retrospectively evaluated biopsies from 55 patients diagnosed with IP using PCR-bead-based multiplex genotyping. In 61.8% of the patients included in the study (34/55) HPV-DNA sequences were identified (19 high-risk and 15 low-risk strains), with HPV16 (84.2%) and HPV54 (53.3%) being the most frequent subtypes. On the other hand, Fulla et al.[21], using PCR analysis for HPV-DNA detection and p16INK4a analysis on biopsies from 79 patients with SNIP reported HPV-DNA identification in only 4 patients (5.1%), all of whom were associated with HPV11.

The mechanisms by which HPV may contribute to the development and progression of sinonasal IP include the expression of viral oncoproteins E6 and E7, which inactivate key proteins involved in cell cycle regulation – p53, p16, p21, p27, cyclin D1, and pRb – thereby leading to loss of control over cellular proliferation[22,23]. Additionally, HPV may stimulate signalling pathways such as EGFR (epithelial growth factor receptor) and Akt/mTOR, promoting aberrant cell growth and potentially the malignant transformation of lesions[13].

The involvement of Epstein-Barr virus in the onset of sinonasal IP remains controversial, with some studies supporting this association, while

other authors have found no clear connection between the existence of this virus and IP[24-27].

More and more studies highlight the role of angiogenic and proliferative factors in the occurrence of rhinosinusal inverted papilloma. Proliferative factors such as proliferating cell nuclear antigen (PCNA), BCL-2, Ki67, epithelial growth factor receptor (EGFR), and pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and osteopontin have shown involvement in the development and progression of IP[4]. In all cases, a significant association with the presence of high-risk potentially oncogenic HPV strains was observed.

DIAGNOSTIC PROTOCOL AND CHALLENGES

Clinical evaluation

In 4-23% of cases, lesions may be asymptomatic and discovered during routine check-up[17]. In the remaining cases, patients usually present with unilateral nasal obstruction, anteroposterior rhinorrhea, hyposmia, headache, recurrent epistaxis or facial pressure/pain.

Objectively, the clinical and endoscopic nasal examination may reveal a unilateral, cauliflower-like, irregular tumor mass, most frequently located on the lateral nasal wall, occupying the ethmoidal labyrinth, in contact with the frontal recess and middle turbinate. The mass is firm in consistency, highly vascularized, slightly bleeding on contact, with a reddish or pink-yellowish colour. When the inverted papilloma is mainly located in the maxillary sinus, only a small formation may be visible in the nasal cavity, while the tumor mass itself predominantly occupies the sinus cavity[18]. The most common site of origin is the lateral nasal wall[28].

Imaging

From an imaging perspective, the cranio-facial computed tomography (CT) is the first-line investigation in the evaluation of inverted papilloma. It frequently reveals features such as unilateral localization, a heterogeneous appearance of the lesion, the presence of calcifications or areas of intratumoural sclerosis, as well as signs of local invasion with bone destruction[5,29]. The origin of the tumor may be suggested by the presence of a bony spur or areas of hyperostosis on the sinus wall[30].

Magnetic resonance imaging (MRI) plays a complementary role, being particularly useful in cases where the tumor extends beyond the bony boundaries or when malignant transformation is suspected. It provides a more accurate assessment of the extension of the lesion and a clearer differentiation between tumoral and inflammatory tissue. On T1-weighted sequences, the lesion appears hypointense, with strong and often homogeneous contrast enhancement, displaying a characteristic cerebriform pattern[5]. On T2 sequences, the tumor usually presents an isointense or hypointense signal relative to the surrounding mucosa[5,29].

As a novel diagnostic approach for these lesions, the Radiomics method can be mentioned. When applied to ENT imaging, especially on CT sequences, it enables the extraction of relevant quantitative parameters from nasosinusal lesions, thereby facilitating the differentiation between entities with similar radiological appearance, such as nasal polyps and inverted papillomas. This contributes to optimising diagnosis and therapeutic decisions[31].

Histopathological examination

The name of this type of papilloma derives from the fact that the tumor presents a digitiform epithelial proliferation that invaginates into the chorion, giving it this inverted appearance. Macroscopically, it resembles an irregular, firmer, friable polyp, with

Table 1. Krouse staging for inverted papilloma.

Stage	Description
T1	Tumor confined exclusively to the nasal cavity, without extension into the sinuses. No associated malignancy.
T2	Tumor involving the osteomeatal complex, ethmoid cells, and/or medial portion of the maxillary sinus, with or without involvement of the nasal cavity. No signs of malignancy.
T3	Tumor involving the lateral, inferior, superior, anterior, or posterior walls of the maxillary sinus, sphenoid sinus, and/or frontal sinus, with or without involvement of the medial portion of the nasal cavity, maxillary sinus, or ethmoid cells. No signs of malignancy.
T4	Tumor with extranasal/extrasinus extension, involving adjacent structures such as the orbit, intracranial compartment, or pterygomaxillary space. Malignant transformation present.

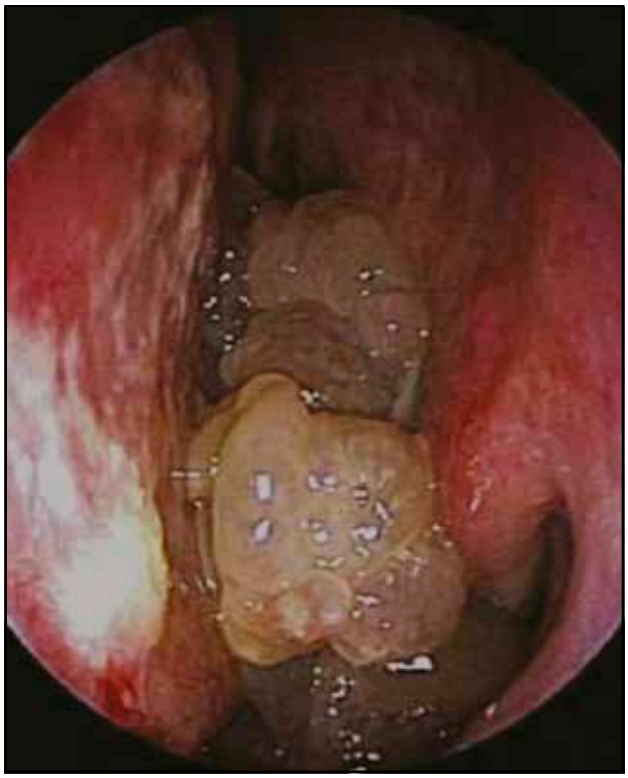


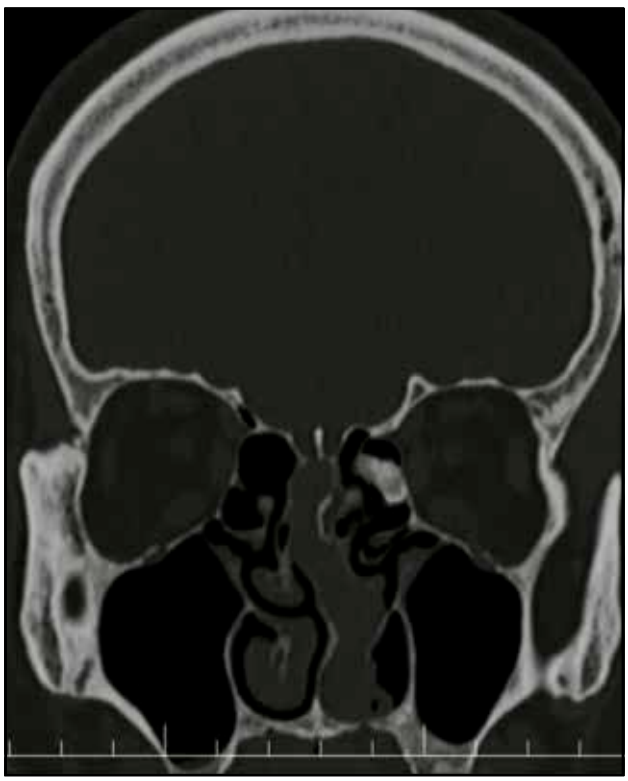
Figure 1. Endoscopic image of the tumor mass located in the left nasal cavity.

a tendency to bleed upon contact, whose colour varies from pale whitish-pink to red.

Microscopically, the characteristic appearance is a hypercellular thickening of the surface epithelium, with invaginations into the underlying stroma. Crypts with a subepithelial arrangement are present and remain in continuity with the surface epithelium. Mucus-filled microcysts may exist in the tumor epithelium. The cells show minimal nuclear atypia and typical mitoses located in the basal layer. The stroma often presents chronic inflammatory changes with areas of fibrosis[32], but it lacks the myxoid-edematous character seen in allergic polyposis, as well as the eosinophilia characteristic of the latter[33].

Staging

The Krouse classification (Table 1) is a staging system used to assess the extent of sinonasal inverted papilloma (IP) in the nasal cavity and paranasal sinuses based on radiological findings. It helps guide therapeutic decisions and assess the risk of postoperative recurrence[3,34]. In addition, although less commonly used, classifications by Han[35], Kamel[36], Cannady[37] or Dragonetti can also be encountered. However, it should be noted that, while the Krouse classification is the most widely used, it was developed before endoscopic



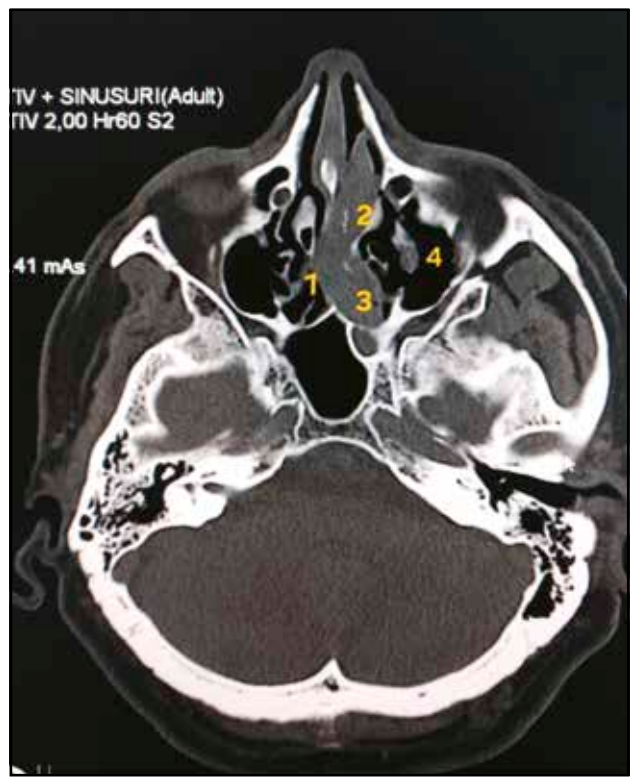


Figure 2. Cranio-facial CT scan, coronal and axial sections, performed in 2025, showing: 1 – erosion of the nasal septum; 2 – tumor mass at the level of the left middle turbinate and middle meatus; 3 – posterior ethmoid cells occupied by the tumor mass; 4 – left maxillary sinus without pathological changes.

sinus surgery became widely employed in the treatment of inverted papillomas. Thus, Lisan et al.[5] conducted a meta-analysis of 13 studies from the literature to see if there is a connection between Krouse staging and the tumor recurrence rate. The results were surprising, as the highest recurrence rate (51%) was found in stages T2-T3, concluding that a direct link between staging and recurrence rate cannot be established. This is because, although this classification is easy to use, it encompasses very heterogeneous groups, especially within the T4 subgroup, which involves the presence of malignancy[38]. In 2020, this classification was proposed to standardize the evaluation and comparison of surgical outcomes.

PERSONAL EXPERIENCE

A 63-year-old patient presented to our ENT Department with worsening left nasal obstruction, which had started approximately 3 years prior to the consultation, accompanied by fronto-orbital headache and rhinorrhea.

The endoscopic examination revealed a vegetative, cauliflower-like formation completely occupying the left middle meatus and partially the left inferior meatus (Figure 1).

The cranio-facial CT scan revealed partial opacification of the left anteroposterior ethmoidal cells and of the left middle meatus, with partial lysis of the ipsilateral middle turbinate and vomer, as well as an area of osteocondensation, which intraoperatively proved to be a fungus ball (Figure 2). We were able to assess the origin and progression of the tumor over a 5-year period by comparing the two CT examinations performed in 2020 and 2025. Initially, in 2020, the small tumor was located on the external portion of the left middle turbinate, without invading the ethmoid (Figure 3). On the 2025 cranio-facial CT scan, the lesion encompassed the middle nasal turbinate, extended into the left anteroposterior ethmoid, partially towards the contralateral nasal cavity through lysis of the bony nasal septum, and it did not bleed on contact. The tumor mass measured approximately 7 × 6 cm (Figure 2).

The tumor was excised via endoscopic sinus surgery under general anesthesia with orotracheal intubation, together with the anterior and middle portions of the left middle turbinate (the suspected site of origin), and with opening of the anteroposterior ethmoid. The excised tissue was sent for histopathological examination (Figure 4). Additionally, a fungal mass of about 5 mm (fungus ball) was ablated from the left posterior ethmoid. Postoperatively, the patient received systemic treatment for 3 days, with a third-generation cephalosporin (IV ceftriaxone 1g every 12 hours), a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties (ketoprofen, 1 ampoule twice daily), and hemostatic to avoid the risk of intra- and postoperative bleeding. Local nasal care was performed daily, with removal of the hemostatic nasal packing 48 hours postoperatively, and discharge occurred on the 4th postoperative day.

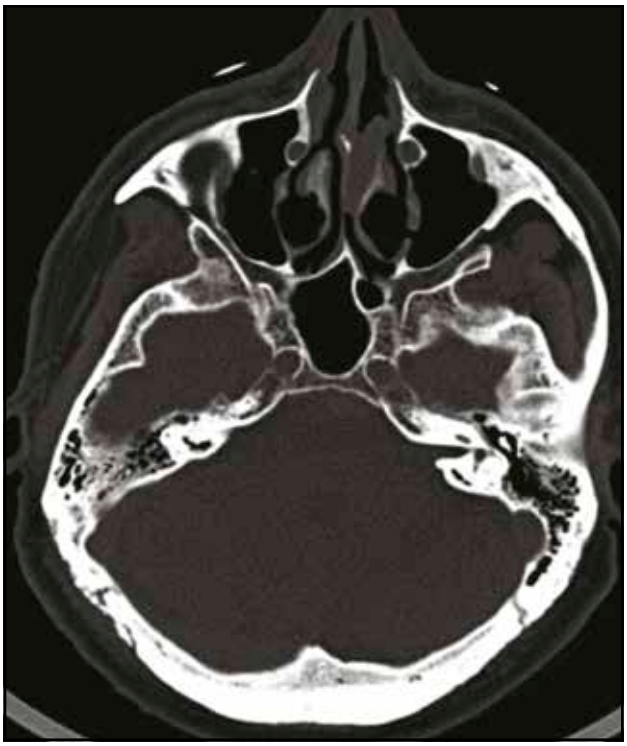


Figure 3. Cranio-facial CT scan, axial section, performed in 2020 – insertion of the nasal tumor, detected at onset, at the level of the external portion of the left middle turbinate, without involvement of adjacent structures.

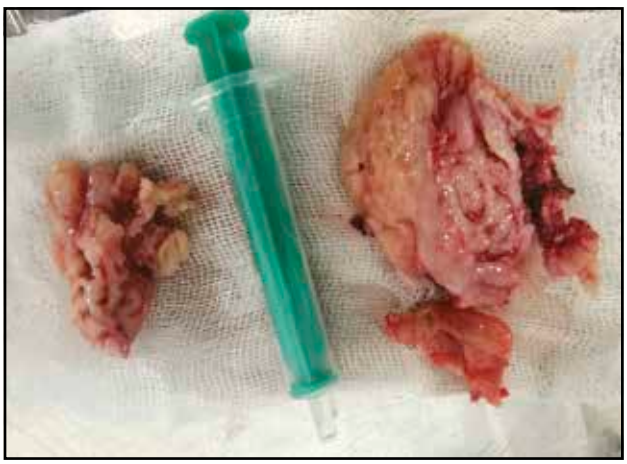


Figure 4. Excised nasal tumor.

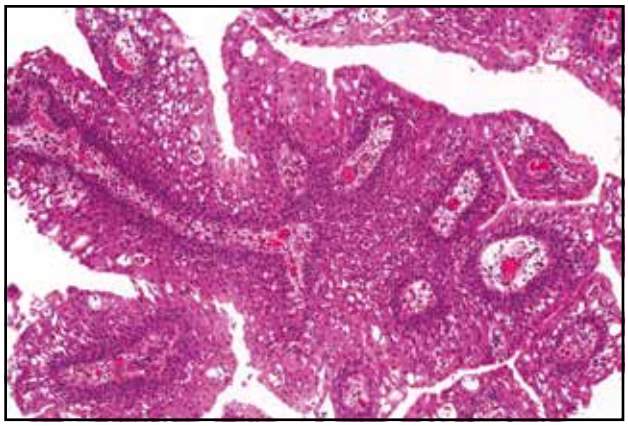


Figure 5. Histopathological examination – epithelium with pseudostratified columnar cells mixed with mucocytes (goblet cells) and microcysts; an endophytic or inverted growth pattern with thickened marked pseudostratified ciliated columnar epithelium growing downward into the underlying stroma (H&E staining, x100).

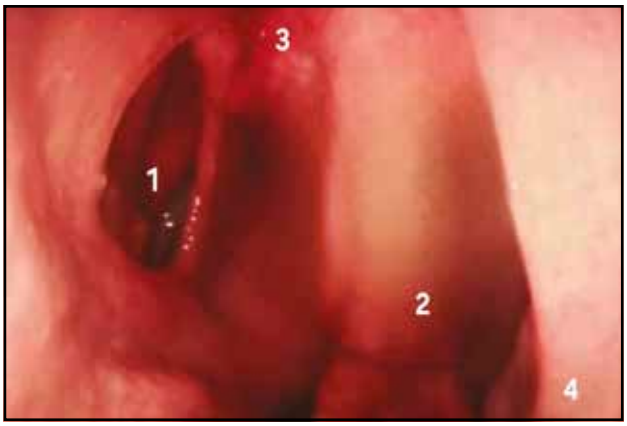


Figure 6. Endoscopic examination 1 month postoperatively: 1 – nasal septum perforation caused by lysis of the bony septum by the tumor formation; 2 – the posterior portion of the left middle nasal turbinate remaining after excision of the tumor mass that encompasses its antero-medial part; 3 – posterior ethmoid region; 4 – internal wall of the left maxillary sinus.

Histological examination with hematoxylin and eosin staining revealed polypoid tissue covered with pseudostratified columnar ciliated epithelium with mixed mucocytes (goblet cells) and occasional intraepithelial mucous cysts. The hyperplastic Malpighian epithelium exhibited endophytic invaginations within the stroma, with aggregates consisting of hyperplastic squamous epithelium and ciliated respiratory epithelium, showing inversion into the underlying connective tissue stroma. The connective tissue cores were fibrocellular in nature, containing chronic inflammatory cells, mainly lymphocytes (Figure 5). The histopathological findings were suggestive of inverted papilloma. Immunohistochemistry revealed weak, mosaic nuclear pattern of p16, Ki67 expressed in basal and parabasal nuclei of the papillary epithelium, and diffuse nuclear positive p63 in the papillary epithelium, a profile that supports the diagnosis of inverted Schneiderian papilloma.

The patient returned for a follow-up 10 days postoperatively, when a sample of secretions from the resection margins was also taken under endoscopic control for HPV DNA genotyping. The follow-up conducted 1 month postoperatively showed favourable local evolution, with no signs of residual tumor tissue or locoregional recurrence (Figure 6).

HPV genotyping did not detect the presence of this virus, being negative for both low-risk and high-risk strains.

The result of the follow-up CT scan performed 60 days postoperatively (Figure 7) and the follow-up endoscopy showed no residual tumor or locoregional recurrence.

Considering the clinical, imaging and histopathological data, the tumor formation was classified as Stage I according to the Krouse staging system.

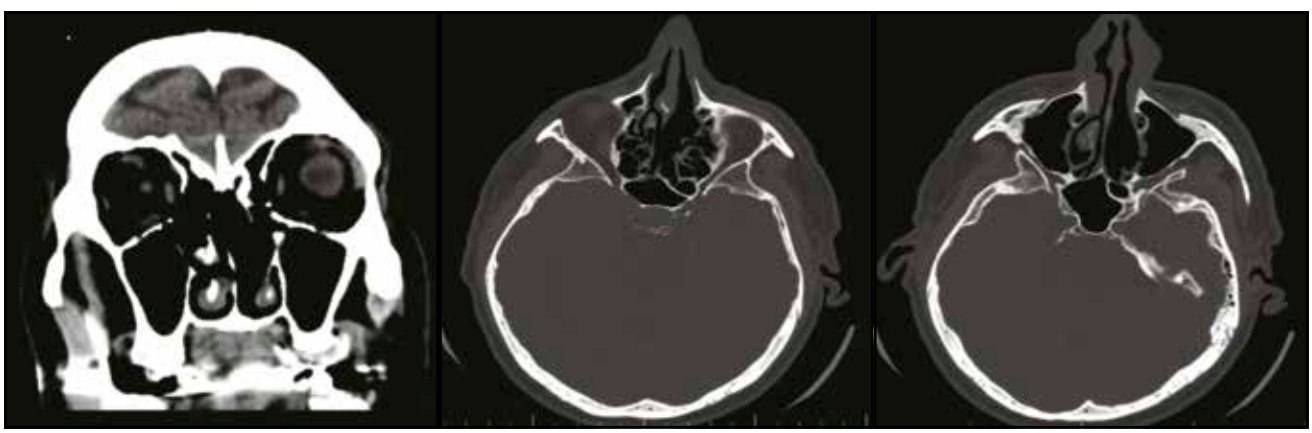


Figure 7. Cranio-facial CT scan at 2 months postoperatively (coronal and axial sections) – no residual tumor, no inflammatory changes in the paranasal sinuses.

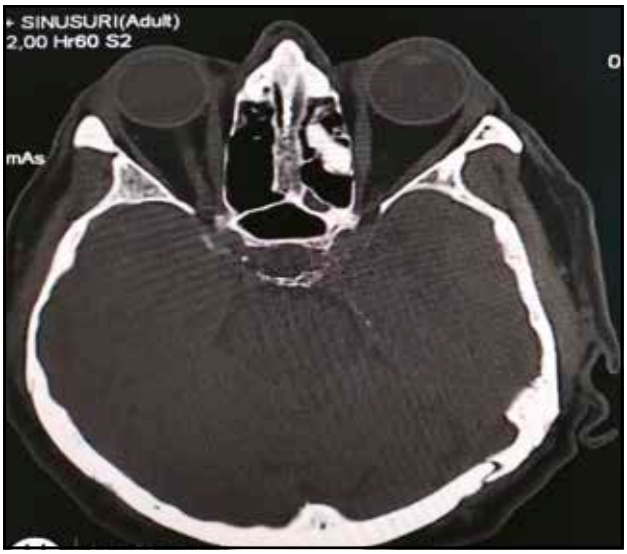


Figure 8. Cranio-facial CT scan (performed in 2025, prior to surgery) – association of fungal sinusitis with involvement of the left posterior ethmoid cells on the same side as the tumor.

The particularities of this case included: erosion of the nasal septum and association with a fungal sinusitis located to 1-2 cells of the posterior ethmoid on the same side (Figure 8).

In the case of this patient, the primary risk factor is smoking, which has been ongoing for almost 45 years.

TREATMENT

The treatment should include complete surgical resection, either through an external approach or endoscopically. Failure to achieve total resection is associated with repeated recurrences, and this hypothesis was first proposed and demonstrated by Ringertz in 1938.

Until the 1990s, the most commonly used technique for large, extensive tumors was medial maxillectomy through lateral rhinotomy with *en bloc* resection of the tumor and the lateral nasal wall, or midfacial degloving[28,32].

In recent decades, the continuous evolution of endoscopic surgical techniques and the development of appropriate working instruments have made the endoscopic approach the main surgical treatment method for this pathology, limiting the use of classical techniques, widely used until the 1990s. At the same time, the endoscopic approach offers significant advantages, such as direct visualization of the lesion, reduced postoperative complications, faster recovery and superior cosmetic outcomes compared to external approaches[39]. Depending on the tumor extension, classical conservative approaches, such as the Caldwell-Luc technique and Denker's rhinotomy, can also be used in combination with nasal endoscopic surgery.

Currently, worldwide, endoscopic surgery tends to become the gold standard in the treatment of sinonasal inverted papillomas, even in cases of advanced disease stages, recurrences or relapses. From the point of view of therapeutic success and prognosis, the chosen surgical approach is crucial, as it influences the rate of local relapses. A limited excision (ethmoidectomy, antrostomy or polypectomy) determines a recurrence rate of 41-78%, compared to medial maxillectomy, which has a recurrence rate of approximately 0-14%[32].

When performed with a correct surgical indication, mainly based on the tumor's stage, and correctly executed by surgeons experienced in endoscopic rhinosinusal surgery, this approach presents a risk and recurrence rate similar to those recorded by open interventions. Considering the stage (Krouse I), the fairly good delimitation and the localization at the level of the left middle turbinate and ethmoid, the surgical intervention in the presented case was performed via an endoscopic endonasal approach.

A definitive contraindication for the endoscopic approach is tumor extension into the frontal sinus and the lateral wall of the maxillary sinus.

Busquets and Hwang discovered significantly lower recurrence rates in the endoscopic approach for inverted sphenoidal papillomas compared to the traditional approach (12% vs. 20%; $p < 0.01$)[40].

Medical treatments such as immunotherapy, chemotherapy (Mitomycin C) and/or antiviral treatments have not yet fully proven their efficacy and are still under investigation.

Moreover, considering that papillomas do not respond to radiotherapy, it should not be used, both due to its ineffectiveness and the risk of malignant transformation of benign lesions. Radiation should be considered a reserve therapeutic method, aimed at cases that have undergone malignant transformation or when there are contraindications to surgical treatment[41].

CLINICAL IMPLICATIONS AND PROGNOSIS

The risk of recurrence of sinonasal inverted papilloma has been and continues to be an intensively discussed and researched topic. Studies conducted over time have reported a recurrence risk varying between 0% and 50%, influenced by several factors such as incomplete resection, tumor localization and origin, tumor extension, histopathological factors, and association with HPV[38,40].

Studies have shown that sinonasal inverted papilloma classified as T3 in the Krouse staging system has a significantly higher risk of postoperative recurrence compared to stage T2. A meta-analytic study conducted by Lisan et al.[38] in 2017 highlighted a 51% higher probability of recurrence for stage T3 compared to T2. Conversely, no significant differences were observed

between stages T1 and T2 or between T3 and T4 in terms of recurrence risk. Additionally, the presence of malignancy in stage T4 can significantly influence the therapeutic approach, requiring careful evaluation of surgical options and the need for adjuvant treatment.

Localization in the frontal sinus has been shown to be an important factor in recurrence development (OR=2.522; p=0.001)[42].

From a histopathological perspective, the presence of severe epidermal hyperplasia, hyperkeratosis and a high mitotic index may represent a negative prognostic factor in terms of the risk of recurrence[43]. Also, the association with the presence of HPV may be an indicator for recurrence[14,15].

In the case of our patient, considering the early stage, localization, the absence of HPV strains and the fact that the patient managed to quit smoking and will come for regular follow-ups, the prognosis is favourable.

An important aspect in the case of a patient with sinonasal inverted papilloma is the postoperative follow-up period. Most specialized studies recommend follow-up for a minimum duration of 5 years[44-46]. A consensus in the evaluation of patients operated for sinonasal IP appears to be follow-up every 3-4 months during the first postoperative year, every 4-6 months in the second year, and subsequently every 6 or 12 months[5].

CONCLUSIONS

Inverted papilloma is a benign tumor that has a high recurrence rate and a tendency to invade adjacent structures. It displays malignant behaviour through its three defining characteristics, namely pronounced local aggressiveness with increased capacity to invade surrounding tissues, including bone, a marked tendency for recurrence and the potential for malignant transformation of the lesion.

The presence of inverted papilloma recurrence in a significant proportion of cases is associated with incomplete tumor resection and may be linked to the development of squamous cell carcinoma. It is important to note the connection between the occurrence of this neoplasm and the presence of a positive HPV infection, with strains 6 and 11 typically found in benign lesions and strains 16 and 18 frequently identified in malignant ones. Since inverted papilloma is considered an intermediate type of lesion, it requires complete *en bloc* excision. The preferred surgical method is endoscopic rhinosinusal surgery. Moreover, involvement of the paranasal sinuses, lacrimal fossa, frontonasal duct and the infraorbital recess of the maxillary sinus is associated with a higher recurrence rate.

Funding: None.

Conflict of interest: The authors have no conflict of interest.

Contribution of authors: All the authors have equally contributed to this work.

Financial discloser: There are no financial disclosures of the authors.

Authors' information

Luciana Arjoca, Student, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: lucianalapusneanu@gmail.com.

Sebastian-Ionut Arjoca, Student, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania. E-mail: arjoca_sebastian@yahoo.com.

Lucian Lapusneanu, Consultant ENT Specialist, ENT Department, Braila County Emergency Clinical Hospital, Braila, Romania, E-mail: llapusneanu@gmail.com. ORCID: https://orcid.org/0000-0002-3817-4837.

Daniela Mihalache, MD, Pathologist, Department of Anatomopathology, Braila County Emergency Clinical Hospital, Braila, Romania. E-mail: cytopath_office@yahoo.com.

REFERENCES

1. Hong SL, Kim BH, Lee JH, Cho KS, Roh HJ. Smoking and malignancy in sinonasal inverted papilloma. Laryngoscope. 2013;123(5):1087-91. DOI: 10.1002/lary.23876.
2. Sauter A, Matharu R, Hormann K, Naim R. Current advances in the basic research and clinical management of sinonasal inverted papilloma (review). Oncol Rep. 2007;17(3):495-504.
3. Barnes L, Eveson J, Reichart P, Sidransky D. Patholoy and genetics of head and neck tumours. In: World Health Organization Classification of Tumors. 3rd Edition. Volume 9. IARC Press: Lyon (France); 2005.
4. Sunkara PR, Saraswathula A, Ramanathan M Jr. Etiology of sinonasal inverted papilloma: An update. Laryngoscope Investig Otolaryngol. 2022;7(5):1265-73. DOI: 10.1002/lio2.821.
5. Lisan Q, Laccourreye O, Bonfils P. Sinonasal inverted papilloma: From diagnosis to treatment. Eur Ann Otorhinolaryngol Head Neck Dis. 2016;133(5):337-41. DOI: 10.1016/j.anorl.2016.03.006.
6. Hyams V.J. Papillomas of the nasal cavity and paranasal sinuses. A clinicopathological study of 315 cases. Ann Oto Rhinol Laryngol. 1971;80(2):192-206. DOI: 10.1177/000348947108000205.
7. Phillips PP, Gustafson RO, Facer GW. The clinical behavior of inverted papilloma of the nose and paranasal sinuses: report of 112 cases and review of the literature. Laryngoscope. 1990;100(5):463-9. DOI: 10.1288/00005537-199005000-00004.
8. d'Errico A, Zajacova J, Cacciatore A, Boffetta P, Moccia C, Bianchi C, et al. Occupational risk factors for sinonasal inverted papilloma: a case-control study. Occup Environ Med. 2013;70(10):703-8. DOI: 10.1136/oemed-2013-101384.
9. Sham CL, Lee DLY, van Hasselt CA, Tong MCF. A case-control study of the risk factors associated with sinonasal inverted papilloma. Am J Rhinol Allergy. 2010;24(1):e37-e40. DOI: 10.2500/ajra.2010.24.3408.
10. Barbieri PG, Tomenzoli D, Morassi L, Festa R, Fernicola C. Sino-nasal inverted papillomas and occupational etiology. G Ital Med Lav Ergon. 2005;27(4):422-6.
11. Dictor M, Johnson A. Association of inverted sinonasal papilloma with non-sinonasal head-and-neck carcinoma. Int J Cancer. 2000;85(6):811-4. DOI: 10.1002/(sici)1097-0215(20000315)85:6<811::aid-ijc17>3.0.co;2-3.
12. Li X, Wang D, Yin D. Clinical characteristics and recurrence predictors of sinona-

sal inverted papilloma: a retrospective cohort study. Front Oncol. 2025;15:1537905. DOI: 10.3389/fonc.2025.1537905.

13. Gupta R, Rady PL, Sikora AG, Tyring SK. The role of human papillomavirus in the pathogenesis of sinonasal inverted papilloma: a narrative review. Laryngoscope Investig Otolaryngol. 2020;5(6):1121-6. DOI: 10.1002/lio2.2178.
14. Lawson W, Schlecht NF, Brandwein-Gensler M. The role of the human papillomavirus in the pathogenesis of Schneiderian inverted papillomas: an analytic overview of the evidence. Head Neck Pathol. 2008;2(2):49-59. DOI: 10.1007/s12105-008-0048-3.
15. Sham CL, To KF, Chan PKS, Lee DLY, Tong MCF, van Hasselt CA. Prevalence of human papillomavirus, Epstein–Barr virus, p21, and p53 expression in sinonasal inverted papilloma, nasal polyp, and hypertrophied turbinate in Hong Kong patients. Head Neck. 2012;34(4):520-33. DOI: 10.1002/hed.21772.
16. Syrjanen K, Syrjanen S. Detection of human papillomavirus in sinonasal papillomas: systematic review and meta-analysis. Laryngoscope. 2013;123(1):181-92. DOI: 10.1002/lary.23688.
17. Respler DS, Jahn A, Pater A, Pater MM. Isolation and characterization of papillomavirus DNA from nasal inverting (schneiderian) papillomas. Ann Otol Rhinol Laryngol. 1987;96(2 Pt 1):170-3. DOI: 10.1177/000348948709600206.
18. Weber RS, Shillitoe EJ, Robbins KT, Luna MA, Batsakis JG, Donovan DT, et al. Prevalence of human papillomavirus in inverted nasal papillomas. Arch Otolaryngol Head Neck Surg. 1988;114(1):23-6. DOI: 10.1001/archotol.1988.01861300270009.
19. Liu Y, Duan L, Tian J, Wang Y, Hu C, Li J, et al. Role of the Akt/mTOR signaling pathway in human papillomavirus-associated nasal and sinonasal inverted papilloma. Acta Biochim Biophys Sin (Shanghai). 2017;49(12):1067-74. DOI: 10.1093/abbs/gmx108.
20. Frasson G, Cesaro S, Cazzador D, Padoan A, Schiavo M, Zanotti C, et al. High prevalence of human papillomavirus infection in sinonasal inverted papilloma: a single-institution cohort of patients. Int Forum Allergy Rhinol. 2020;10(5):629-35. DOI: 10.1002/alr.22539.
21. Fulla M, Szafarowski T, Frias-Gomez J, Orłowski M, Bienkowski M, Alvarez Marcos C, et al. Human papillomavirus and factors associated with recurrence in sinonasal inverted papillomas from Poland and Spain. Head Neck Pathol. 2020;14(3):758-67. DOI: 10.1007/s12105-019-01125-y.
22. Altavilla G, Staffieri A, Busatto G, Canesso A, Giacomelli L, Marioni G. Expression of p53, p16INK4A, pRb, p21WAF1/CIP1, p27KIP1, cyclin D1, Ki-67 and HPV DNA in sinonasal endophytic Schneiderian (inverted) papilloma. Acta Otolaryngol. 2009;129(11):1242-9. DOI: 10.3109/00016480802620647.
23. Yeo-Teh NSL, Ito Y, Jha S. High-risk human papillomaviral oncogenes E6 and E7 target key cellular pathways to achieve oncogenesis. Int J Mol Sci. 2018;19(6):1706. DOI: 10.3390/ijms19061706.
24. Suntornlohanakul R, Wanlapakorn N, Vongpunsawad S, Thongmee T, Chansaenroj J, Poovorawan Y. Seroprevalence of anti-EBV IgG among various age groups from Khon Kaen Province, Thailand. Asian Pac J Cancer Prev APJCP. 2015;16(17):7583-7. DOI: 10.7314/apjcp.2015.16.17.7583.
25. Nukpook T, Ekalaksananan T, Teeramatwanich W, Patarapadungkit N, Chaiwiriyakul S, Vatanasapt P, et al. Prevalence and association of Epstein-Barr virus infection with sinonasal inverted papilloma and sinonasal squamous cell carcinoma in the northeastern Thai population. Infect Agent Cancer. 2020;15:43. DOI: 10.1186/s13027-020-00308-5.
26. Dunn ST, Clark GD, Cannon TC, Min KW. Survey of sinonasal inverted papillomata for Epstein-Barr virus. Head Neck. 1997;19(2):98-106. DOI: 10.1002/(sici)1097-0347(199703)19:2<98::aid-hed3>3.0.co;2-p.
27. Gaffey MJ, Frierson HF, Weiss LM, Barber CM, Baber GB, Stoler MH. Human papillomavirus and Epstein-Barr virus in sinonasal Schneiderian papillomas. An in situ hybridization and polymerase chain reaction study. Am J Clin Pathol. 1996;106(4):475-82. DOI: 10.1093/ajcp/106.4.475.
28. Vrabec DP. The inverted Schneiderian papilloma: a 25-year study. Laryngoscope. 1994;104(5 Pt 1):582-605. DOI: 10.1002/lary.5541040513.
29. Momeni AK, Roberts CC, Chew FS. Imaging of chronic and exotic sinonasal disease: review. AJR Am J Roentgenol. 2007;189(6 Suppl):S35-S45. DOI:10.2214/AJR.07.7031.
30. Bhalla RK, Wright ED. Predicting the site of attachment of sinonasal inverted papilloma. Rhinology. 2009;47(4):345-8. DOI: 10.4193/Rhin08.229.
31. Guo M, Zang X, Fu W, Yan H, Bao X, Li T, et al. Classification of nasal polyps and inverted papillomas using CT-based radiomics. Insights Imaging. 2023;14:188. DOI: 10.1186/s13244-023-01536-0.
32. Anghel I, Anghel A, Barbuceanu E, Stefan C, Matei R. Papilomul invertit. Practica Medicala. 2011;6(1):30-4.
33. Calcaterra TC, Thompson JW, Paglia DE. Inverting papillomas of the nose and paranasal sinuses. Laryngoscope. 1980;90(1):53-60. DOI: 10.1288/00005537-198001000-00006.
34. Krouse JH. Development of a staging system for inverted papilloma. Laryngoscope. 2000;110(6):965-8. DOI: 10.1097/00005537-200006000-00015.
35. Han JK, Smith TL, Loehrl TA, Toohill RJ, Smith MM. An evolution in the management of sinonasal inverting papilloma. Laryngoscope. 2001;111(8):1395-1400. DOI: 10.1097/00005537-200108000-00018.
36. Kamel RH. Transnasal endoscopic medial maxillectomy in inverted papilloma. Laryngoscope. 1995;105(8 Pt 1):847-53. DOI: 10.1288/00005537-199508000-00004.
37. Cannady SB, Batra PS, Sautter NB, Roh HJ, Citardi MJ. New staging system for sinonasal inverted papilloma in the endoscopic era. Laryngoscope. 2007;117(7):1283-7. DOI: 10.1097/MLG.0b013e31803330f1.
38. Lisan Q, Moya-Plana A, Bonfils P. Association of Krouse Classification for sinonasal inverted papilloma with recurrence: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg. 2017;143(11):1104-10. DOI: 10.1001/jamaoto.2017.1686.
39. Keshma HK, Kessis T, Hruban RH, Wu TC, Zinreich SJ, Shah KV. Human papilloma virus in sinonasal papilloma and squamous cell carcinoma. Laryngoscope.1992;102(9):973-6. DOI: 10.1288/00005537-199209000-00003.
40. Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134(3):476-82. DOI: 10.1016/j.otohns.2005.11.038.
41. Tusaliu M, Romaniuc AD, Bucur C, Lozba A, Vulpe M, Vrejoiu CA. Abordul clasic versus abordul endoscopic in papilomul inversat nazosinuzal. ORL.ro. 2022;57(4):28-33. DOI: 10.26416/ORL.57.4.2022.7287.
42. Kim DY, Hong SL, Lee CH, Jin HR, Kang JM, Lee BJ, et al. Inverted papilloma of the nasal cavity and paranasal sinuses: a Korean multicenter study. Laryngoscope. 2012;122(3):487-94. DOI: 10.1002/lary.22495.
43. Katori H, Nozawa A, Tsukuda M. Histopathological parameters of recurrence and malignant transformation in sinonasal inverted papilloma. Acta Otolaryngol. 2006;126(2):214-8. DOI: 10.1080/00016480500312554.
44. Lund VJ, Stammberger H, Nicolai P, Castelnuovo P, Beal T, Beham A, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinology Suppl. 2010;22:1-143.
45. Carta F, Blancal JP, Verillaud B, Tran H, Sauvaget E, Kania R, et al. Surgical management of inverted papilloma: approaching a new standard for surgery. Head Neck. 2013;35(10):1415-20. DOI: 10.1002/hed.23159.
46. Philpott CM, Dharamsi A, Witheford M, Javer AR. Endoscopic management of inverted papillomas: long-term results—the St. Paul's Sinus Centre experience. Rhinology. 2010;48(3):358-63. DOI: 10.4193/Rhin09.105.