SINONASAL INVERTED PAPILLOMA

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ABSTRACT

Introduction: Based on the etiology, sinonasal inverted papilloma is a multifactorial disease and with unknown of definite cause, the progression of the disease is benign but aggressive that it can destroy the surrounding area, as well as the rate of recurrence and transformation into malignancy is quite high. **Objective:** To determine the etiology, epidemiology, pathophysiology, and management of sinonasal inverted papilloma inverted. **Conclusion:** Inverted papilloma is a sinonasal benign tumor whose etiology is still unknown, but several studies say it is associated with HPV infection, Epstein-Barr virus, angiogenesis, exposure to cigarette smoke, and exposure to welding fumes. Early diagnosis is necessary given the progression of the disease tends to destructive to the surrounding organs.

Keywords: Sinonasal Inverted Papilloma, tumor.

DEFINITION

Sinonasal inverted papilloma tumor is a benign tumor originating from the Schneiderian mucosa. Schneiderian mucosa is the mucous membrane that covers the inside of the sinus cavities, a ciliated columnar epithelium with goblet cells.[1,2] Histologically, the Schneiderian membrane is composed of thin layers of ciliated columnar epithelium with goblet cells and vascularized connective tissue.[3-6] Scheneiderian papillomas consist of inverted papilloma (IP), Schenideriann oncocytic papilloma (cylindrical cell papilloma, columnar cell papilloma) and fungiform papilloma (exophytic papilloma, septal papilloma, squamous papilloma). However, there are some studies who still consider these three lesions as one entity, named under general terms such as papilloma, papillomatosis, or Schneiderian papilloma.[1]

The most common location for inverted papillomas is the nasal cavity and paranasal sinus mucosa, and they can be present in several places at once, making it difficult to determine the initial location of IP. Specific sites of IP include the maxillary sinus (48%), lateral wall of the nose and ethmoid sinuses (28%), and frontal sinus (2.5%).[7] Inverted papilloma is a tumor that can transform and become locally aggressive, has a tendency to erode the surrounding bone, and has a high recurrence rate, as well as a tendency to develop into malignancy, namely squamous cell carcinoma.[2,3]

The mucous membranes found within the nose and paranasal sinuses exhibit a distinct composition, consisting of two distinct types known as the respiratory part and olfactory part. Specifically, the respiratory part of the mucosa can be observed lining the lower two-thirds of the nasal septum, as well as the lateral wall of the nose located beneath the superior turbinate. Furthermore, it extends to cover the floor of the nasal cavity, reaching from the nasal lumen deep into the nasal region and ascending to encompass the upper one-third of the nasopharynx. In addition to these regions, the respiratory part of the mucosa extends to the paranasal sinuses via their respective ostia. It is also connected to the epithelium of the lacrimal duct and the auditory tube. Moreover, it is intimately associated with the olfactory epithelium in an upward direction, while anteriorly in the lumen nasi, it is connected to the skin of the nasal vestibule.[4]

The olfactory mucosa, also referred to as the Schneiderian membrane, covers specific areas within the nasal cavity in a distinct manner. It can be observed lining the upper one-third of the nasal septum, extending to the roof of the nasal cavity, and encompassing the lateral wall of the superior turbinate as well as the area above it.

Comprising the mucous membrane are olfactory cells that exist in a bipolar form. These specialized cells play a crucial role in our sense of smell. Situated on the surface of this mucous membrane, one can find olfactory hairs, which further contribute to the detection and perception of odors. These olfactory hairs facilitate the capture of scent molecules, enabling the olfactory cells to transmit signals to the brain for interpretation.

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Alongside the olfactory cells, the mucous membrane is composed of supporting cells that provide structural support and assist in the proper functioning of the olfactory system. Additionally, there are basal cells present within the mucosa, which contain a distinct yellow pigment. These basal cells are involved in the continuous regeneration and replenishment of the olfactory cells, ensuring the ongoing functionality of the olfactory system.

In summary, the olfactory mucosa, also known as the Schneiderian membrane, lines specific regions of the nasal cavity, including the upper portion of the nasal septum, the roof of the nasal cavity, the lateral wall of the superior turbinate, and the area above it. It consists of specialized olfactory cells in a bipolar configuration, which are accompanied by olfactory hairs, supporting cells, and basal cells containing a yellow pigment. Together, these components contribute to our ability to perceive and interpret various scents.[8] Movement of the palate carries mucous and bring particles to the oropharynx, part of them are swallowed toward the outside of the nasal cavity.[4]

The frontal sinuses originate from cells located in either the frontal recess or the ethmoid infundibulum. It is important to note that the development of the frontal sinuses commences after birth, typically around the age of 8 to 10 years. Over time, these sinuses gradually grow and expand, reaching their maximum size before an individual reaches the age of 20 years.

Interestingly, the right and left frontal sinuses often exhibit asymmetry, meaning that they are not identical in size or shape. In many cases, one of the frontal sinuses tends to be larger than the other. This asymmetrical nature is a common characteristic observed in individuals, and it contributes to the uniqueness of each person's nasal anatomy.

In summary, the frontal sinuses emerge from cells found within the frontal recess or the ethmoid infundibulum. Their development commences during childhood, typically around the age of 8 to 10 years, and they continue to grow until they reach their maximum size by the age of 20 years. It is noteworthy that the right and left frontal sinuses often display asymmetry, with one sinus being larger than the other. This natural variation adds to the individuality of each person's nasal structure. The ethmoid sinuses have the most varied shapes and considered as the most important, because they can be a focus of infection for other sinuses. In adults, the ethmoid sinuses are pyramidal in shape with their base posteriorly. Behind the posterior ethmoid sinuses is adjacent to the sphenoid sinuses. The sphenoid sinuses is divided in two by a partition called the intersphenoid septum.[5]

The function of the paranasal sinuses is as a regulator of air conditioning, additional space to heat and regulate the humidity of inspired air. The other function is as a thermal insulator, as a heat buffer, protects the orbit and cerebral fossa from the changing temperature of the nasal cavity change, help balance the head, help with sound resonance, as a damper for air pressure's change, and also help mucous production.[5]

Epidemiology

Sinonasal malignancies are rare, only 3% of malignancies in the head and neck and about 1% of malignancies throughout the body. The incidence of sinonasal malignancy is more common in Asia and Africa than in the United States. In Asia, sinonasal malignancy ranks second as most frequently malignancy of the head and neck, after nasopharyngeal carcinoma. Rifki stated the data he collected from public hospitals from 10 big cities in Indonesia, the frequency of sinonasal tumors is 9.3-25.3% of ENT malignancies and ranks second after malignant nasopharyngeal tumors.[6,7]

Based on the 2005 WHO classification, Scheneiderian papillomas consist of IP, oncocytic papilloma, and exophytic papilloma, with an incidence rate of 80.33%, 9.84%, and 9.84% respectively among sinonasal papillomas.[9] The incidence rate of IP in sinonasal cavity tumor is between 0.4-7%, with an incidence of IP about 0.2-1.5 cases per 100,000 people per year.[10] The ratio between men and women is 4:1. Inverted papilloma occurs frequently in adults and is diagnosed in the 40-70 year age group, and is rare in children and adolescents.[8,9]

Etiology

The cause of IP is not yet fully understood, but there are some known contributing factors, such as rhinosinusitis, nasal polyp growth, smoking, allergies, and occupational exposures. There is evidence suggesting a viral origin for IP recurrence and carcinoma transformationThe human papillomavirus (HPV) has garnered attention as a potential viral agent for several decades, with researchers investigating its possible association with various diseases. One notable area of study has focused on the role of HPV in the development of certain cancers. In a study conducted by Kashima et al., the presence of HPV DNA was identified in pathology specimens of inverted papilloma (IP) and sinonasal squamous cell carcinoma using a technique called polymerase chain reaction (PCR). The study revealed that specific HPV types, namely types 6, 11, 16, and 18, were of particular interest due to their potential risk levels in relation to the development of IP and sinonasal squamous cell carcinoma.

Types 6 and 11 of HPV were categorized as low-risk types, while types 16 and 18 were considered high-risk. This distinction is crucial, as it implies that these high-risk HPV types may have a greater propensity to cause IP and sinonasal squamous cell carcin

oma compared to the low-risk types. The presence of HPV in these pathology specimens indicates a potential association between the virus and the development of these malignancies.

Further investigations conducted by McKay et al. and Cheung et al. have provided additional insights into the role of HPV in the progression of IP and the initiation of its pathogenesis. McKay et al. discovered that HPV can contribute to the malignant transformation of cells, suggesting that the virus may play a pivotal role in the development of IP into a cancerous condition. Additionally, Cheung et al. demonstrated that HPV is involved in the early stages of IP pathogenesis, indicating that the virus may have a role in the initiation of the disease.

Collectively, these studies highlight the significance of HPV as a potential viral agent in the development of IP and sinonasal squamous cell carcinoma. The detection of HPV DNA in pathology specimens, coupled with the identification of specific high-risk HPV types, provides valuable evidence for its potential involvement in the pathogenesis and progression of these diseases. By elucidating the relationship between HPV and these malignancies, further research may uncover new avenues for prevention, diagnosis, and treatment strategies. However, conflicting evidence has also been presented, such as Jenko et al.'s study, which suggested that HPV may be incidental rather than a direct cause. Some researchers have investigated the mechanism by which HPV could cause IP by studying its effect on the expression of p53 and p21. P53 is a tumor suppressor that helps protect against DNA damage and mutations, while p21 regulates cell cycle arrest during growth. HPV's oncoproteins, E6 and E7, interfere with the normal function of p53 and p21, which could contribute to the development of IP.

Several factors have been linked to the growth of IP, including cellular factors involved in angiogenesis such as osteopontin (OPN), angiomotin, and Vascular Endothelial Growth Factor (VEGF). Recent studies have shown that IP tissue has an increased number of neutrophils, macrophages, eosinophils, CD8+ T cells, and T-reg cells, indicating the importance of immune response in IP development. Chronic inflammation has also been suggested as a possible cause of IP, as supported by studies conducted by Yoon et al. and Roh et al. In addition, occupational exposure to organic solvents, welding fumes, and nickel compounds have been linked to IP. Sham et al. found a correlation between IP and exposure to certain industries, as well as outdoor work. Furthermore, smoking and occupational exposure have been shown to contribute to the development of IP, with smokers having a higher risk of malignant transformation compared to non-smokers, as demonstrated by studies conducted by Sham et al.

DIAGNOSIS

IP is often diagnosed in an advanced stage, typically 1-4 years after the onset of sinonasal symptoms. Diagnosis is established through anamnesis, physical examination, pathological examination, and radiological examination. Nasal obstruction is the primary symptom in IP, with 78-100% of cases reporting it. Other symptoms include a runny nose, epistaxis, increased nasal area volume, facial pain, headache, hyposmia or anosmia, and/or facial pain. In some cases, IP is asymptomatic and discovered incidentally. Endoscopic examination of the nasal cavity reveals a lobulated, reddish-gray tumor with a raspberry-like appearance, which is harder than an inflammatory polyp. Palpation of the tumor is friable and bloody. Histologically, IP is characterized by an endophytic growth pattern consisting of thick epithelial cell proliferation that grows toward the stroma. Inflammatory cells, particularly neutrophils and macrophages, frequently migrate through the epithelium. In the tissue of inverted papilloma (IP), neutrophils are the primary inflammatory cells, followed by CD4+ T cells, eosinophils, CD8+ T cells, and FoxP3+ T-reg cells, indicating the presence of an inflammatory response. Microscopic examination reveals distinctive features of IP, characterized by hyperplastic bands of basement membrane and a closed epithelium that grows inwardly into the underlying stroma, a phenomenon known as endophytic growth. The epithelium itself is multilayered, comprising approximately 5 to 30 cells and is composed of a mixture of squamous or ciliated columnar cells along with goblet cells.

The dominant type of epithelium observed in IP is non-keratinizing squamous epithelium, although respiratory epithelium may also be present in some cases. Mitotic figures, which are indicative of cell division, are generally scarce within the IP tissue. If mitoses are identified, they are primarily located in the basal and parabasal epithelium layers, suggesting active cellular proliferation in those regions. In certain instances, there may be the presence of exophytic and/or endophytic components within the IP tissue, indicating additional variations in the growth patterns of the tumor.

Overall, the composition and microscopic characteristics of IP tissue provide valuable insights into its pathogenesis. The presence of neutrophils and various T-cell subtypes suggests an ongoing inflammatory process within the tissue. The hyperplastic bands of basement membrane and the closed, multilayered epithelium with specific cellular compositions contribute to the distinct structure of IP. Understanding these microscopic features can aid in the accurate identification and diagnosis of IP and may also provide clues regarding its underlying mechanisms and potential treatment approaches

Microscopically, oncocytic papilloma exhibits a growth pattern that is both exophytic and endophytic.

The epithelium is multilayered, with a thickness of approximately 2-8 cells, and comprises tall columnar cells with swollen, finely granular cytoplasm. On the other hand, fungiform papilloma is characterized by papillary leaves with a fine fibrovascular core that is covered by epithelium, with a thickness ranging from 5-20 cells, which can vary from squamous to transitional (intermediate) to ciliated pseudostratified columnar cells.

Table 1. Classification of Inverted Papilloma[9]

Papilloma	Fungiform	Inverted	Oncocytic
Synonym	Septal	Ringertz	Cylinder, columnar
Prevalence	50%	47%	3-5%
Location	Nasal sentun	Lateral wall of nasal and paranasal sinus	Lateral wall of nasal and paranasal sinus
Epithelial growth pattern	Everted, exophytic	Infolded, endophytic	-
Microscopic	Thick squamous epithelium and respiratory epithelium with leaf-like form	Thick squamous epithelium with muco-cyst contain mucous	Cytoplasmic of eosinophil coated epithelium between mucous-filled cysts
Age group	Young	50-60 years old	30-80 years old
Malignancy	35% transform to squamous cell carcinoma	Locally aggressive, spread to orbital sinus, nasopharynx, meningeal, 3-24% transform to squamous cell carcinoma	14-19% potentially transform to malignancy

Radiological assessment serves two main purposes, detecting the location of the tumor and determining its extension. In the case of IP, CT scans typically reveal unilateral isodense homogeneous lesions centered on the medial nasal meatus. Approximately 20% of cases show microcalcifications within the lesions, which aid in diagnosis. Bone erosion is also common. However, CT imaging can be insufficient for estimating excessive lesion size and does not allow for adequate preoperative planning due to difficulty in differentiating the lesion from surrounding inflammation or the presence of retention. Inverted papilloma is not known to induce bone remodeling and resorption like malignant tumors, but it can cause hyperostosis in the form of a cone or plaque. A study by Sham et al. found that a CT scan showing focal hyperostosis or an elongated bony prominence with a narrow base has a positive predictive value of 100% in identifying the site of attachment of inverted papilloma. However, approximately 20% of CT images are inaccurate in defining tumor extension. MRI is an excellent imaging modality for delineating the centrifugal range of IP due to its ability to differentiate between tumors with post-obstructive inflammatory changes. It can also identify the cerebriform pattern, which is a sign of intracranial extension of the tumor. Several classifications of IP have been published, including Krouse's classification based on radiologically assessed tumor extension, which is widely used in the international literature. Other less widely used classifications include those developed by Han (2001), Kamel (2005), Cannady (2007), and Drag-onetti (2011).

Table 2. Krouse Classfication[10]

	Staging of Krouse System for Inverted Papilloma
T1	Tumour limited to the nasal cavity without extension to the sinuses. Not associated with malignancy.
T2	Tumour involving the osteomeatal complex, ethmoidal sinus, and/or the medial portion of the maxillary sinus, with/without involvement of the nasal cavity. Not associated with malignancy.
T3	Tumour involving the lateral, inferior, superior, anterior or posterior walls of the maxillary sinus, sphenoid sinus, and/or frontal sinus, with/without involvement of the medial portion of the maxillary sinus, ethmoid sinus, or nasal cavity. Not associated with malignancy.
T4	All tumours with extranasal/extrasinus extension involved or adjacent structures, such as the orbital, intracranial compartment, or pterygomaxillary space. All tumours associated with malignancy.

Therapy

Currently, the standard IP management techniques involve surgery, radiotherapy, or a combination of both. Historically, various surgical approaches have been used, including non-endoscopic endonasal, limited external (Caldwell-Luc), radical external (lateral rhinotomy or midfacial degloving with en bloc resection), and endoscopic endonasal. The primary goals of surgery are to relieve symptoms and examine the entire specimen for possible carcinoma. Preoperative medical therapy, including antibiotics and corticosteroids, is often given to reduce inflammation and bleeding during surgery.

Table 3. Operative Approach Based on Tumour Extension[8]

Involvement	Suggestion of Surgery Approach
Septum	Endoscopic endonasal
Lateral wall of nasal cavity	
Anterior/posterior ethmoid	
Sphenoethmoid & sphenoid space	
Maxillary sinus (medial, superior, or posterior wall)	
Frontal cavity and fronal sinus	
Lateral wall of frontal sinys	Endoscopic endonasal + frontal osteoplastic flap (bicoronal approach)
Maxillary sinus (anterior, inferior, or lateral wall)	Endoscopic endonasal + Caldwell-Luc approach
Extrasinus extension	External (paralateronasal approach)
Related carcinoma	

However, no conclusive data exist on the efficacy of this approach. While external surgery remains the gold standard for sinonasal tumor removal, it has several drawbacks, including scarring, complications, long hospital stays, and high costs. Limited conservative surgery may be an option for some lateral lesions. Endoscopic resection has several advantages, such as shorter hospital stays, less blood loss, shorter operation times, and lower morbidity. However, endoscopic surgery is limited to certain types of lesions and may not be sufficient for tumors attached to the base of the skull. The choice of surgical approach depends on the stage of the disease and the location of the tumor. In some cases, radiation therapy may be considered as a treatment option, particularly in cases of associated carcinoma or when surgery is not possible. The average dose of postoperative radiation therapy is 56 Grays, while exclusive radiation therapy for inoperable patients is within 61 Grays. Surgery followed by radiation therapy appears to be more effective in cases of carcinoma

Complication

Intracranial extension of inverted papilloma can lead to symptoms such as headache, proptosis, and seizure. Surgical resection of sinonasal papilloma may result in complications such as blepharitis, diplopia, and intermittent dacryocystitis, especially in patients who undergo lateral rhinotomy approaches and medial maxillectomy. Ectropion may also develop due to scar tissue pulling the lower eyelid down. Surgery that exposes the skull base can cause CSF leaks.
It is important to note that these complications can significantly affect a patient's quality of life and may require additional medical interventions. For example, crusting can cause discomfort and difficulty breathing, while infection can lead to further health complications. Naso-cutaneous fistula, on the other hand, can cause discharge from the site of surgery and may require surgical repair
Vestibular stenosis is a common complication of the degloving procedure, which involves creating an incision on the nasal skin and detaching it from the underlying tissues. This can cause narrowing of the nasal vestibule, leading to breathing difficulties and an increased risk of infection. Similarly, oroantral fistula, which is an abnormal connection between the oral cavity and the maxillary sinus, can occur during or after surgery and may require further intervention to repair
Endoscopic resection, while less invasive than other surgical approaches, can still lead to serious complications. For instance, CSF leaks, which occur when the protective fluid surrounding the brain and spinal cord escapes, can result in severe headaches, meningitis, and other neurological problems. Orbital complications, such as periorbital hematoma and optic nerve damage, can cause vision problems and even blindness. Bleeding, infection, and synechiae formation, which is the abnormal adhesion of tissue, can also occur after endoscopic resection and may require additional treatments to manage.
Therefore, it is important for patients to be aware of these potential complications before undergoing surgery for inverted papilloma. Close monitoring and prompt intervention can help manage these complications and improve patient outcomes. All of these complications can significantly affect the patient's quality of life by interfering with normal nasal function

Prognosis

The post-treatment follow-up protocol included a comprehensive clinical examination and flexible endoscopy, with the possibility of a biopsy to prevent recurrence. MRI scans were conducted regularly during follow-up, except in cases where the IP septum had been completely removed, making clinical surveillance easier. If a recurrence was suspected or the sinus cavities could not be visualized clearly using flexible endoscopes, CT and MRI scans were conducted more frequently. Some authors recommend an MRI every 4 months for 1 year, followed by an MRI every 6 months for 4 years in cases of synchronous squamous cell carcinoma. According to several studies, only 30% of relapses are symptomatic, while 70% are detected through clinical and radiological follow-up. The recommended follow-up frequency is at least every 3-5 years. Recurrence rates were found to be 8.5% for less than

3 years and 26.1% for more than 3 years in a study of 578 patients. Recurrence rates of 11% under 5 years and 44% after 5 years were reported in another study. Additionally, some articles documented recurrences occurring up to 15 years after treatment, prompting a prolonged follow-up. It is essential to maintain long-term follow-up care after a diagnosis of inverted papilloma due to the risk of developing squamous cell carcinoma, which may manifest several years after the initial diagnosis. In order to detect any potential recurrence or malignancy, regular check-ups are necessary. During the first year, patients are usually monitored every three to four months, with subsequent follow-up appointments scheduled every four to six months in the second year. After the second year, appointments are typically scheduled every six to twelve months. The importance of continued surveillance cannot be overstated, as early detection and treatment of any potential complications or recurrence are crucial in ensuring the best possible outcomes for patients.

According to several studies, incomplete resection often causes recurrence, usually at the site of the initial IP, within two years of surgery. Recurrence rates varied between 0% to 50%, according to Busquets' meta-analysis, with a mean recurrence rate of 15% after a median follow-up of 44 months across all stages. Sbrana et al. conducted a study in Brazil involving 49 cases of IP and found that the recurrence rate was 34.09%, with an average recurrence time of approximately 24.6 months and a malignant transformation rate of 13.64%. These findings suggest that the high rate of recurrence and malignant transformation of IP may be due to limited access to healthcare systems in developing countries, resulting in the late-stage detection of many IP cases (T3 and T4)

Table 4. Prognosis of Inverted Papilloma According to Cannady[10]

Group	Location and Displacement of Inverted Papilloma	Recurrence Rate
A	Inverted papilloma is limited to the nasal cavity, ethmoid sinus, medial to the maxillary sinus	3,0%
B	Inverted papilloma with lateral involvement of the maxillary sinus, sphenoid sinus, or involvement of frontal sinus	19,8%
C	Inverted papilloma with extrasinus extension	35,3%

Conclusion

Inverted papilloma (IP) is a benign sinonasal tumor, whose exact cause is still unknown, although various studies suggest a link with HPV infection, angiogenesis, exposure to cigarette smoke, and welding fumes. Early detection is vital to prevent the disease from progressing, as it can cause damage to the surrounding organs. The clinical symptoms of IP include nasal blockage, runny nose, epistaxis, headache, and loss of sense of smell. A diagnosis can be made based on the patient's medical history, physical examination, pathological examination, and radiological examination (CT or MRI scan). Tumor staging is performed using the Krouse classification, while pathological examination is the gold standard. Surgery is the primary treatment option for IP, with radiation therapy and a combination of therapies as additional options. Various surgical approaches, such as endonasal endoscopic, endonasal non-endoscopic, limited external (Caldwell-Luc), and radical external (lateral rhinotomy or midfacial degloving with en bloc resection), are available, but endoscopic surgery appears to be the most effective. The recurrence rate of IP can vary up to 50%, with an average of 15% recurrence at 44 months of follow-up. Inverted papillomas have a tendency to transform into malignant tumors at a rate of 13.64%

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