

N Thapa

Ganesh Man Singh Memorial Academy
of ENT and Head and Neck Studies,
TU Teaching Hospital,
Kathmandu, Nepal

Correspondence to

Dr. Narmaya Thapa
Associate Professor
Dept. of ENT-HNS
Tribhuvan University Teaching
Hospital/Maharajgunj, Kathmandu
Email: naramayat@yahoo.com

Diagnosis and Treatment of Sinonasal Inverted Papilloma

Sinonasal inverted papilloma is a rare locally aggressive benign tumour having high propensity for recurrence and association with synchronous and metachronous malignancies. Literatures were reviewed. CTScan and or MRI are mandatory for extent and diagnosis of tumour. Endoscopic medial maxillectomy have been found to have better results (less recurrence rate), however, total excision with normal tissue is necessary to prevent recurrence.

INTRODUCTION:

According to the World Health Organization, inverted papilloma (IP) is defined as a benign epithelial tumor composed of well-differentiated columnar or ciliated respiratory epithelium having variable squamous differentiation.¹ Embryologically, the ectodermally derived epithelium of IP originating from the Schneiderian mucosa of the nasal cavity is distinct from the endodermally derived mucosa of the upper respiratory tract.² It has many synonyms such as villiform cancer, Schneiderian papilloma, transitional cell papilloma, cylindrical cell papilloma, papillary sinusitis, epithelial papilloma, squamous papillary epithelioma, papillomatosis, endophytic papilloma etc.^{3,4} It has a long history dating over 150 years. In 1854, it was first described by Ward and named schneiderian papillomas in honor of C. Victor Schneider, who in the 1600s identified nasal mucosa origin from ectoderm.⁵ In 1938, Ringertz coined the term "inverted papilloma," based on its histological findings of inversion of the epithelium into underlying stroma.⁶ Inverted papillomas are relatively uncommon tumors of the nasal cavity comprising approximately 0.5% to 4% of all primary nasal tumors. Its incidence ranges from 0.75 to 1.5 cases per 100,000 per year. They occur approximately 15th as often as inflammatory polyps. There is a male predominance 3:1, and it affects primarily Caucasians.⁷ Most patients are usually diagnosed in the 5th to 7th decade with average age of 53 years. However, it has been reported in children and adolescent, and elderly group also.⁸ It is a benign but locally aggressive tumour having high chance of recurrence and high risk of association with synchronous as well as metachronous malignancies.⁷ Aetiology Its exact aetiology is still uncertain. Studies using in situ hybridization and polymerase chain reaction (PCR) have detected human papillomavirus (HPV) in upto 86% of inverted papillomas.^{9,10} Mostly HPV 6, 11, 16 and 18 have been found. The presence of HPV DNA in inverted papilloma have been found to be associated with higher chance of recurrence and malignant transformation.^{11,12} Some studies also reported association of Epstein Barr virus with inverted papillomas but others have defeated it.^{10,13,14} Other various factors such as smoking, exposure to certain chemicals, allergy and chronic inflammation have also been implicated but has not been proved yet.

SITE OF ORIGIN:

The commonest site of origin of this tumour is lateral wall of nasal cavity, then medial wall of maxillary sinus. Less commonly it arises from ethmoid, sphenoid and frontal sinuses. Isolated involvement of sphenoid sinus have been reported by many authors.¹⁵⁻²² Besides nose and paranasal sinuses inverted papilloma arising from lacrimal sac and temporal bone have also been reported.²³⁻²⁵

CLINICAL FEATURES:

The clinical presentation of sinonasal inverted papilloma depends upon the sites of involvement. However, the commonest symptom of sinonasal inverted papilloma is progressive unilateral nasal obstruction. Other symptoms include blood mixed nasal discharge, headache, facial pain, frequent clearing of throat, decreased or loss of smell, epiphora or symptoms suggestive of sinusitis. Inverted papilloma generally occurs unilateral, but the bilateral involvement of the sinonasal tract has been reported in less than 1 to 9% patients.²⁵⁻²⁷ A recent study by Visvanathan et al reported 10 cases of inverted papilloma with intracranial extension.²⁸ On examination, a pinkish polypoidal smooth or lobulated mass with papillary surface located lateral to the middle turbinate in the nasal cavity is a suggestive diagnosis of inverted papilloma (Fig.1).



Fig. 1: Typical Endoscopic picture of inverted papilloma

Septum may be pushed to opposite side. However, sometimes clinically there may be difficulty to differentiate inverted papilloma from other nasal masses. In our previous study on nasal masses 1 case was diagnosed clinically as simple nasal polyp but histopathological report came out to be inverted papilloma. Similarly clinically diagnosed three cases of inverted papilloma were histopathologically reported as inflammatory polyps in two and angiofibroma in one.²⁹ Depending upon the extent of tumour other signs such as proptosis and facial swelling may be present.

INVESTIGATIONS:

Computed tomography and magnetic resonance imaging (MRI) are the techniques of choice for pretreatment staging of neoplasms of the sinonasal tract. The CT-based determination of the locations of the areas of focal hyperostosis corresponded to the actual tumor origin in 89.1% cases of inverted papilloma. Especially in cases with focal hyperostosis within the frontal, maxillary, sphenoid, and posterior ethmoid sinuses, areas of focal hyperostosis corresponded to the origin of tumor without exception (Fig. 2).³⁰ CT scans can be used to differentiate focal



Fig. 2: Coronal CT image in a patient with inverted papilloma shows localized cone-shaped hyperostosis of the superior wall of the posterior ethmoid sinus (white arrow).

hyperostosis from diffuse bone thickening, which is usually associated with chronic paranasal sinusitis.³¹ Other changes in bone that have been detected using CT scanning in patients with inverted papilloma include intratumoral calcification, thinning, bowing, and erosion.^{32,33} A unilateral mass within the nasal cavity or paranasal sinuses with a surface configuration that appears lobulated on CT is a new sign that strongly suggests inverted papilloma as a primary diagnosis and also suggests inverted papilloma in patients with tumor recurrence (Fig.3).³² Sometimes CT Scan may not be sufficient to differentiate inverted papilloma from other soft tissue lesions. In such cases RI is needed. A columnar pattern is a reliable MRI indicator of IP and reflects its histological architecture (positive predictive value of 95.8%). The combination of this finding with the absence



Fig. 3: Coronal CT Scan of a patient with inverted papilloma showing lobulated soft tissue density in the left maxillary sinus extending to nasal cavity

of extended bone erosion allows for the confident discrimination of IPs from Malignant tumours.³⁴ A sinonasal mass with a convoluted cerebriform pattern (CCP) on T2- or enhanced T1-weighted images suggests inverted papilloma as a histologic

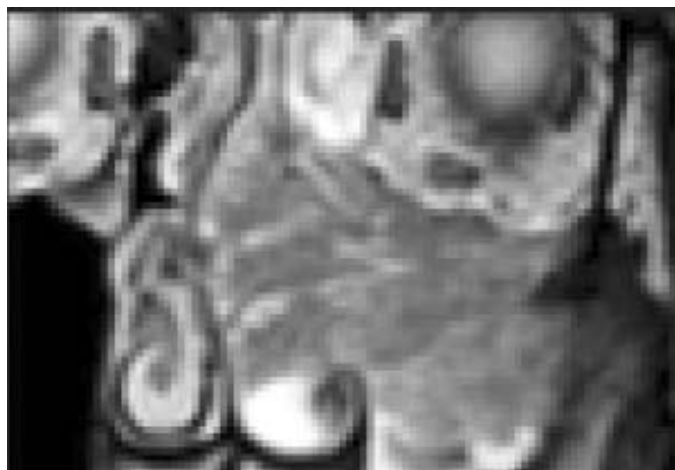


Fig 4: Characteristic MR imaging appearance of a CCP in IP. Coronal T2-weighted MR image showing alternating hypointense and hyperintense striations throughout the tumor involving the left maxillary sinus and nasal cavity.

diagnosis (Fig.4). Necrosis in a mass with such an appearance strongly suggests coexistent carcinoma.³⁵ Jeon et al found CCP as a reliable MR imaging feature of sinonasal IPs to differentiate them from various malignant sinonasal tumors with the overall accuracy of 89%. However, even the presence of a diffuse CCP throughout the tumor on MR imaging does not always guarantee the diagnosis of benign IPs, because it also can be seen in IPs concomitant with SCC or other malignant tumors. A focal loss of a CCP might be a clue to a preoperative prediction of IPs concomitant with malignancy.³⁶ A biopsy is mandatory to obtain a definitive diagnosis. In microscopic examination the proliferated epithelium is found to be invaginated towards stroma (Fig 5).

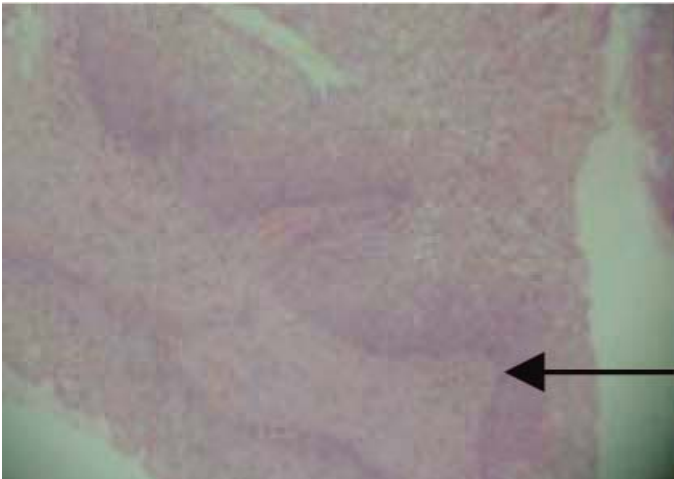


Fig.5:Histological picture of inverted papilloma proliferated epithelium invaginated towards stroma shown by arrow.

TREATMENT:

Wide excision of the tumour with normal surrounding tissue is necessary to prevent recurrence of inverted papilloma. Lateral rhinotomy or midfacial degloving approach with medial maxillectomy was the surgical treatment for this tumour. However, since 1980s endonasal endoscopic or microendoscopic techniques have been largely applied to resect this tumour. Lateral rhinotomy approach gives adequate exposure to resect tumour from nasal cavity and sinuses and bone but the disadvantages are postoperative scar, epiphora, CSF leak. The scar problem can be avoided by midfacial degloving approach. Its disadvantages include insufficient access to more distant areas, such as frontal, superior ethmoid, sphenoid sinuses, orbital and complications include vestibular stenosis, oroantral fistula and epistaxis. This approach can be combined with endoscopic approach to prevent scar as well as to clear disease from frontal and sphenoid sinuses. Midfacial degloving is particularly useful for inverted papillomas that are bilateral nasal in origin. Endonasal endoscopic approach reduces complications of external approaches but if the tumour is extensive it may not be adequate to clear all the tumour. However, many literatures have shown less recurrence rate in endoscopic approach ranging from 3-17% in comparison to the external approach with recurrence rate of 18-24%.^{2,37-41} Although traditionally endoscopic surgery is used more for small lesions recently, however, a new technique has been described for treatment of massive tumors with attachments within the maxillary sinus. It is called SSES (Sequential Segmental Endoscopic sinus Surgery). This involves sequential excision of larger tumors into segments, four segments usually. First, the nasal cavity; second, the middle meatus, including portions of the ostiomeatal complex; third, the maxillary sinus ostium and antrum along with the maxillary sinus medial wall if an endoscopic medial maxillectomy is performed; and then the frontal or sphenoid sinus.⁴² The contraindications to a purely endoscopic resection of inverted papillomas include the concomitant presence of squamous cell carcinoma, massive skull base erosion, intradural or intraorbital extension, and extensive involvement of the frontal sinus. Frozen sections should be obtained in all types of surgeries to confirm negative margins and bone should be removed from underlying sites of attachment. Radiation therapy

has been used as an alternative treatment; however, its use should be reserved for inverted papilloma associated with squamous cell carcinoma.^{43,44} Definitive radiotherapy may also be used to successfully treat patients with incompletely resectable inverted papilloma.⁴⁴⁻⁴⁶ It has been suggested that as an adjunct to surgical excision in aggressive HPV-related disease, adjunctive treatments, usually in the form of immunomodulation, Interferon can be used.⁴⁷ Its mechanism of action is by producing P56 which inhibits HPV DNA replication through direct interaction with the origin-binding protein E1 of several strains of HPV.⁴⁸ For recurrent respiratory papillomatosis, interferon and topical cidofovir are recommended to lower recurrence rate.⁴⁹ The tetravalent HPV vaccine Gardasil has been recently developed and found to be effective against HPV types 6, 11, 16 and 18.¹⁸ There are no studies in the literature describing the use of these treatments for sinonasal inverted papilloma.

CONCLUSION:

Besides routine nasal endoscopy, CT Scan and or MRI are necessary for diagnostic clues and extent of inverted papilloma. Surgery whether external approach or endoscopic wide excision is necessary to prevent recurrence of the tumour. Other modalities of treatment should be reserved for extensive and recurrent tumour and studies should be done in future to detect efficacy of antiviral agents in the treatment of inverted papillomas.

REFERENCES:

1. Shanmugaratnam K, Sobin LH. The World Health Organization histological classification of tumours of the upper respiratory tract and ear. A commentary on the second edition. *Cancer* 1993;71:2689-97
2. Pasquini E, Sciarretta V, Farneti G, et al. Inverted papilloma: report of 89 cases. *Am J Otolaryngol* 2004;25:178-85.
3. Bielamowicz S, Calcaterra TC, Watson D. Inverting papilloma of the head and neck: the UCLA update. *Otolaryngol Head Neck Surg.* 1993;109: 71-6.
4. Iqbal SM, Khan IA, Khan IZ et al. Inverted papillomas of the nose and sinuses: Clinical presentations, Surgical treatment and outcome. *Journal of Surgery Pakistan (International).* 2008;13 (2): 85-87.
5. Kramer R, Som ML. True papilloma of the nasal cavity. *Arch Otolaryngol.* 1935;22-43.
6. Ringertz N. Pathology of malignant tumors arising in the nasal and paranasal cavities and maxilla. *Acta Otolaryngol (Stockh).* 1938;27 (Suppl):31-42.
7. Sauter A, Matharu R, Horman K, et al. Current advances in the basic research and clinical management of sinonasal inverted papilloma (review). *Oncol Rep* 2007; 17: 495-504.
8. Roland DE. Inverted papilloma of the nose and paranasal sinuses in childhood and adolescence. 2009; 95 (1): 17 - 23.
9. Hwang CS, Yang HS. Detection of human papillomavirus (HPV) in sinonasal inverted papillomas using polymerase chain reaction (PCR). 1998 Sep-Oct;12(5):363-6.
10. Gaffey MJ, Frierson HF, Weiss LM et al. Human papillomavirus and Epstein-Barr virus in sinonasal Schneiderian papillomas. An in situ hybridization and polymerase chain reaction study. 1996 Oct;106(4):475-82.

11. Ogura H, Fukushima K, Watanabe S. A high prevalence of human papillomavirus DNA in recurrent nasal papillomas. *1996 Sep*;45(3):162-6.
12. Hoffmann M, Klose N, Gottschlich S. Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. *2006 Jul 28*;239(1):64-70.
13. Macdonald MR, Le KT, Freeman J et al. A majority of inverted sinonasal papillomas carries Epstein-Barr virus genomes. *1995 May 1*;75(9):2307-12.
14. Dunn ST, Clark GD, Cannon TC, Min KW. Survey of sinonasal inverted papillomas for Epstein-Barr virus. *1997 Mar*;19(2):98-106.
15. Yiotakis I, Psarommatas I, Manolopoulos L et al. Isolated inverted papilloma of the sphenoid sinus. *Journal of Laryngology & Otology (2001)*,115:3:227-230.
16. Nishio S, Samoto K, Takeshita I et al. Inverting papilloma of the sphenoid sinus: report of two cases. *J Clin Neurosci. 2001 Mar*;8(20):168-70.
17. Cho HJ, Kim JK, Kim K. Endoscopic surgery for inverted papilloma originating from the sphenoid sinus and related clinical characteristics. *Acta Otolaryngol 2008*;128: 1120 - 1125.
18. Joseph AJ, Moorthy R, Saleh H. Endoscopic management of inverted papilloma of the sphenoid sinus. *BMJ Case Reports 2009*;10:1136.
19. Lee JT, Bhuta S, Lufkin R et al. Isolated inverting papilloma of the sphenoid sinus. *Laryngoscope 2003*; 113: 41-4.
20. Peters BW, O'Reilly RC, Wilcox, J et al. Inverted papilloma isolated to the sphenoid sinus. *J Otolaryngol Head Neck Surg 1995*; 113: 771-7.
21. Sethi DS. Isolated sphenoid lesions: diagnosis and management. *J Otolaryngol Head Neck Surg 1999*;120: 730-6.
22. Wang ZM, Kanoh N, Dai CF et al. Isolated sphenoid sinus disease: an analysis of 122 cases. *2002 Apr*;111(4):323-7.
23. Raemdonck Tia YE, Van den Broecke CM, Claerhout I et al. Inverted papilloma arising primarily from the lacrimal sac. *2009*; 28 (2-3): 181-184.
24. Weng BM. Schneiderian-type mucosal papillomas of the middle ear and mastoid. *Ann Otol Rhinol Laryngol 1996*; 105:226-33.
25. de Filippis C, Marioni G, Tregnanhi A, Marino F, Gaio E, Staffieri A. Primary inverted papilloma of the middle ear and mastoid. *Otol Neurotol 2002*; 23:555-559.
26. Phillips PP, Gustafson RO, Facer GW. The clinical behavior of inverting papilloma of the nose and paranasal sinuses: report of 112 cases and review of the literature. *Laryngoscope 1990*;100:463-69.
27. Yiotakis J, Hantzakos A, Kandiloros D, Ferekidis E. A rare location of bilateral inverted papilloma of the nose and paranasal sinuses. *2002 Dec*; 40(4):220-2.
28. Visvanathan V, Wallace H, Chumas P et al. An unusual presentation of inverted papilloma: case report and literature review. *2009 Aug 3*:1-4.
29. Pradhananga RB, Adhikari P, Thapa NM et al. Overview of Nasal masses. *Journal of Institute of Medicine 2008*; 30(3):1316.
30. Lee DK, Chung SK, Dhong HJ et al. Focal Hyperostosis on CT of Sinonasal Inverted Papilloma as a Predictor of Tumor Origin. *American Journal of Neuroradiology. 2007 Apr*; 28:618-621.
31. Dammann F, Pereira P M, Laniado M et al. Inverted papilloma of the nasal cavity and the paranasal sinuses: using CT for primary diagnosis and follow-up. *Am J Roentgenol. 1999*; 172: 543-548.
32. Woodruff WW, Vrabec DP. Inverted papilloma of the nasal vault and paranasal sinuses: spectrum of CT findings. *Am J Roentgenol 1994*;162:419-235.
33. Lund VJ, Lloyd GA. Radiological changes associated with inverted papilloma of the nose and paranasal sinuses. *Br J Radiol 1984*; 57:455-61.
34. Maroldi R, Farina D, Palvarini L, Lombardi D, Tomenzoli D, Nicolai P. Magnetic resonance 2004 Sep-Oct;18(5):305-10.
35. Ojiri H, Ujita M, Tada S, et al. Potentially distinctive features of sinonasal inverted papilloma on MR Imaging. *Am J Roentgenol 2000*;175:465-68.
36. Jeon TY, Kim H.J, Chung SK et al. Sinonasal Inverted Papilloma: Value of Convuluted Cerebriform Pattern on MR Imaging. *American Journal of Neuroradiology. 2008 Sept*; 29:1556-1560.
37. Lawson W, Kaufman MR, Biller HF. Treatment outcomes in the management of inverted papilloma: an analysis of 160 cases. *Laryngoscope 2003*;113:1548-56.
38. Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. *Otolaryngol Head Neck Surg 2006*;134:476-82.
39. Tomenzoli D, Castelnuovo P, Pagella F, et al: Different endoscopic surgical strategies in the management of inverted papilloma of the sinonasal tract: experience with 47 patients. *Laryngoscope 2004*; 114: 193-200.
40. Kaza S, Casiano RR. Endoscopic resection of inverted papilloma: University of Miami experience. *Am J Rhinol 2000*;17: 185-190.
41. Kraft M, Kaufmann T, Holzmann D. Long-term results of endonasal sinus surgery in sinonasal papillomas. *Laryngoscope 2003*; 113: 1541-1547.
42. Lee TJ, Huang SF, Lee LA et al. Endoscopic surgery for recurrent inverted papilloma. *Laryngoscope 2004*;114:106-112.
43. Weissler MC, Montgomery WW, Turner PA et al. Inverted papilloma. *Ann Otol Rhinol Laryngol 1986*;95: 215-221.
44. Gomez JA, Mendenhall, WM, Tannehill SP, et al. Radiation therapy in inverted papilloma of the nasal cavity and paranasal sinuses. *Am J Otolaryngol 2000*; 2: 174-8.
45. Mendenhall W, Hinerman RW, Malyapa R. et al. Inverted Papilloma of the Nasal Cavity and Paranasal Sinuses. *American Journal of Clinical Oncology. 2007 Oct.*; 30(5):560-563.
46. Mendenhall WM, Million RR, Cassisi NJ et al. Biologically aggressive papillomas of the nasal cavity: the role of radiation therapy. *Laryngoscope. 1985*; 95: 344-347.
47. Gallagher TQ, Derkay SC. Pharmacotherapy of recurrent respiratory papillomatosis: an expert opinion. *Expert Opin Pharmacother 2009*; 10: 645-55.
48. Ternezi F, Saikia P, Sen, G. Interferon-inducible protein, P56, inhibits HPV DNA replication by binding to the viral protein E1. *EMBO 2008*; 27: 3311-21.
49. Pawlita, M, Gissmann L. Recurrent respiratory papillomatosis: indication for HPV vaccination? *Dtsch Med Wochenschr 2009*; 134: S100-2.