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Case Report

Nasal-type Natural Killer/T-cell Lymphoma Occurring at the Site from Which a Sinonasal Inverted Papilloma was Previously Resected: A Rare Case Report

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Abstract

Objectives: Sinonasal inverted papillomas (SNIPs) are benign and account for 0.5%-7% of sinonasal tumors. However, SNIPs have the potential for recurrence and malignant transformation. The most common histologic type of malignant transformation of SNIPs is squamous cell carcinoma, and it is rarely associated with other pathological types of malignancy. Herein, we present a unique case of nasal-type natural killer (NK)/T-cell lymphoma occurring at the site from which a SNIP was previously resected.

Methods: A 58-year-old male nonsmoker had a left SNIP and underwent tumor excision by the endoscopic approach. Postoperatively, SNIP recurrence was not observed in routine follow-up. Thirteen years later, at the age of 71 years, he reported blood-tinged discharge from the left nose for 1 month and was diagnosed with nasal-type NK/T-cell lymphoma occurring at the site from which the SNIP was previously resected. He subsequently underwent tumor excision by the endoscopic approach and adjuvant concurrent chemoradiotherapy (CCRT).

Results: The patient tolerated treatment for nasal-type NK/T-cell lymphoma well. Recurrence of nasal-type NK/T-cell lymphoma was not observed during 30 months of follow-up after therapy.

Conclusion: Based on our research, this is the first reported case of nasal-type NK/T-cell lymphoma occurring at the site from which a SNIP was previously resected. In this case, awareness and early diagnosis, followed by endoscopic excision and adjuvant CCRT, provided good treatment results. This report expands the spectrum of reported SNIP-associated malignancy and emphasizes the importance of considering the malignant transformation of SNIPs and close, prolonged (preferably life-long) follow-up.

Keywords: Nasal-type Natural Killer/T-cell Lymphoma; Sinonasal Inverted Papilloma; Endoscopic Surgery; Concurrent Chemoradiotherapy

Abbreviations

IP: Inverted Papilloma; SNIP: Sinonasal Inverted Papilloma; SCC: Squamous Cell Carcinoma; NK: Natural Killer; CT: Computed Tomography; CCRT: Concurrent Chemoradiotherapy; HPV: Human Papillomavirus; MRI: Magnetic Resonance Imaging; SUVmax: Standardized Uptake Value.

Introduction

Inverted papillomas (IPs) were first described by Ward in 1854 [1,2]. IPs are benign and rare epithelial tumors categorized as

Schneiderian papillomas. The sinonasal tract, middle ear, kidney, ureter, bladder, and urethra are all possible areas for IP occurrence [3,4]. The annual incidence of sinonasal inverted papillomas (SNIPs) is between 0.2 and 1.5 per 100,000 population [1,2]. SNIPs account for 0.5%–7% of sinonasal tumors, have the potential to recur, and have malignant characteristics, including atypia, dysplasia, and carcinoma *in situ* [1,4,5]. The most common histologic type of SNIP-associated malignancy, whether synchronous or metachronous, is squamous cell carcinoma (SCC), and it is extremely rare for SNIPs to be associated with malignancies of different pathologies [2,6].

An extensive literature search revealed only one reported case of coexistence of nasal-type natural killer (NK)/T-cell lymphoma and SNIP [6]. NK/T-cell lymphoma is a rare tumor type commonly occurring in the upper aero-digestive tract, and it accounts for the historical terms lethal midline granuloma and midline reticulosis. In this study, we present a unique case of nasal-type NK/T-cell lymphoma occurring at the site from which a SNIP was previously resected.

Case Report

At the age of 58 years, a Taiwanese male nonsmoker was diagnosed with a left SNIP of stage T3 (classified using the Krouse staging system for SNIP) (Figure 1). He was subsequently treated with tumor excision by the endoscopic approach. During the next 13 years of postoperative follow-up, tumor recurrence was not observed by endoscopy or computed tomography (CT) scans.

Figure 1: A 58-year-old male nonsmoker was diagnosed with a left SNIP (stage T3, classified by Krouse staging system). (A) Endoscopic examination revealed a polypoid tumor (black asterisk) in the left nasal cavity. (B) A CT scan revealed a homogeneous tumor (yellow asterisk) involving the left ostiomeatal complex, left common meatus, and medial and inferior portion of the left maxillary sinus.

At the age of 71 years, 13 years after endoscopic surgery, the patient visited our hospital for the complaint of blood-tinged discharge from the left nose, which had been occurring for 1 month. At the clinic, endoscopic examination identified a hemorrhagic tumor occurring at the site from which the SNIP was previously resected (Figure 2A). A CT scan revealed a tumor involving the left ostiomeatal complex, maxillary sinus, and anterior and posterior ethmoidal sinus (Figure 2B). Subsequently, a biopsy of the tumor was performed. Based on the histopathological features (Figure 3) and the results of immunohistochemical staining (Figure 4), the tumor was consistent with nasal-type NK/T-cell lymphoma. Moreover, a bone scan, CT scan (chest + abdomen + pelvis), and positron emission tomography scan were negative for metastatic disease. Thus, stage IVA nasal-type NK/T-cell lymphoma (classified by the Ann Arbor staging system) was diagnosed.

Figure 2: At the age of 71 years, 13 years after endoscopic surgery, (A) endoscopic examination identified a hemorrhagic tumor (black asterisk) occurring at the site from which the SNIP was previously resected. (B) A CT scan revealed a homogeneous tumor (yellow asterisk) involving the left ostiomeatal complex, maxillary sinus, and ethmoidal sinus.

Figure 3: Histopathological sections of the tumor. (A) At low magnification, the section shows clumps of freshly/recently coagulated blood clots in some places, with early organization or admixed with necrotic debris. Multiple pieces of sinonasal mucosal tissue with edema are also observed in several places, mostly with various degrees of infiltration of chronic inflammatory/lymphoid cells. In some places, this appears as chronic inflammation, whereas elsewhere, denser infiltration with somewhat effacing features is observed. Some scattered suspected abortive or partially lytic B-cell follicles are present (H&E, 20× magnification). (B) At high magnification, the majority of lymphoid cells in the dense infiltration appear to be small, with very few slightly larger cells, and have either dark round nuclei or mild nuclear atypia (occasionally or frequently in different areas, as convoluted or irregular contour). Mitoses are rarely or occasionally seen. (H&E, 400× magnification.).

Figure 4: The immunohistochemical staining findings of lymphoid cells: CD3(+) (A) and CD56(+) (B) in all supposed neoplastic cells; these lymphoid cells are predominant in the effacing growth. CD20(–) in all supposed neoplastic cells (C). The overall features favor nasal-type NK/T-cell lymphoma.

The patient subsequently underwent tumor excision by the endoscopic approach, followed by adjuvant concurrent chemo-radiotherapy (CCRT). The chemotherapy regimen involved cis-platin weekly for five cycles, followed by the SMILE regimen (dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide) monthly for three cycles. Radiotherapy involved apply-ing irradiation at a dose of 54 Gy (27 fractions) to the surgical bed and a dose of 40 Gy (20 fractions) to the bilateral cervical lymph nodes. The patient tolerated the treatment well. Tumor recurrence was not observed in follow-up endoscopy and magnetic resonance imaging (Figure 5) after therapy through the 30-month follow-up point, and the patient has resumed a normal life; however, longer-term follow-up is required to screen for late recurrence.

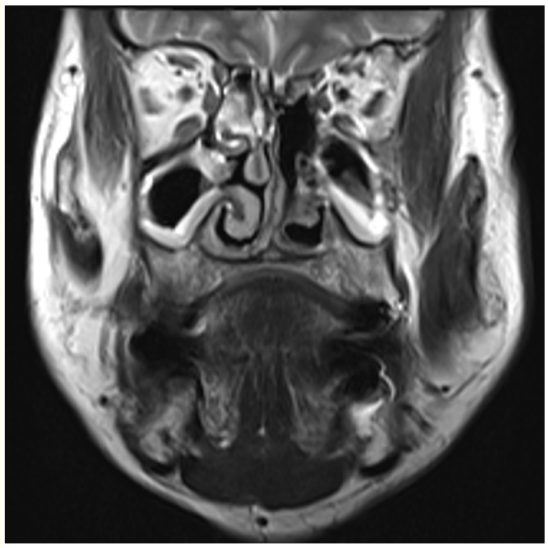

Figure 5: Tumor recurrence was not observed in follow-up magnetic resonance imaging, after therapy, or at the 30-month follow-up point.

Discussion

Although the etiology of SNIPs is still controversial, studies have indicated the potential roles of human papillomavirus (HPV) infection, cell cycle regulatory proteins and angiogenic factors (os-teopontin, vascular endothelial growth factor, and angiomotin), environmental and occupational exposure (smoking, welding, and organic solvents), and chronic inflammation [1,2].

HPV is suspected to play a major role in the pathophysiology of SNIPs, but the data are still contradictory. The wide variation between reports can be attributed to the histologic differences (dysplasia grades): HPV appears to be significantly more frequent in SNIPs showing severe dysplasia or associated carcinoma than in SNIPs with mild or no dysplasia (55% versus 22%) [2]. Nevertheless, although many studies have detected HPV DNA in SNIP specimens, research has not demonstrated that HPV infection is the cause of the development or malignant transformation of SNIPs [1]. Jalilvand., *et al*. suggested that HPV 6 and 11 may participate in the development of SNIPs, but HPV 16 and 18 may play key roles in the malignant transformation of SNIPs [7]. The integration of HPV into the cell genome induces the overexpression of oncoproteins E6 and E7, thereby inactivating cell cycle regulators, such as p16, p21, p27, p53, cyclin D1, and retinoblastoma protein. Relationships among HPV, p53, and p21 and their involvement in the oncogenesis of SNIP-associated malignancy are strongly suspected but have yet to be fully elucidated [2].

A patient's history of smoking seems to be more critical for relapse and dysplasia than for initial SNIP development [1]. The risk factors for synchronous carcinoma of SNIPs have not been determined; however, smoking is one suspected risk factor: a study reported a significant correlation between smoking and synchronous carcinoma [2].

SNIPs have 3 main characteristics that distinguish them from other sinonasal tumors and make them difficult to treat: relatively high local invasiveness, higher recurrence rates in early and late stages, and possible association with carcinoma upon the first diagnosis or recurrence [2,4]. SNIP treatment is surgical, with the main purpose of relieving symptoms and performing a pathological examination of the complete specimen, especially to screen for carcinoma [2]. Endoscopic and traditional surgery have similar success rates, but endoscopic surgery causes less trauma and prevents facial scars; therefore, most surgeons prefer to use endoscopic surgery instead of traditional external approaches. However, endoscopic surgery is indicated only for tumors of limited extension, and an external or combined external/endoscopic approach is indicated for tumors in certain locations [4]. Reaming the underlying bone or performing bone resection can prevent incomplete removal of pathological mucosal fragments [2]. Previous reports have indicated that the location of cone-shaped hyperostosis within the SNIP tissue may predict the origin of SNIPs [4].

The recurrence rate with endoscopic surgery of primary SNIPs is 12.5%. Recurrence is more frequent in residual SNIPs than in primary SNIPs. The inferior outcome of revision SNIP surgery may be due to the increased difficulty of identifying the attachment site of the SNIP because of distorted anatomy and the absence of landmarks [8]. Recurrence is usually within 2 years after surgery [2]. Clinical risk factors for the recurrence and progression of SNIPs include outdoor and industrial occupational exposure (organic solvents, including diethylnitrosamine), smoking, septal deviation, SNIP location (frontal sinus and close proximity to optic nerve and carotid artery), recurrent cases, stage of SNIP-associated SCC, and choice of surgical method [2,4]. By contrast, late recurrence is considered as cancer occurrence at a second location and is more suggestive of viral etiology. In addition, the onset of associated carcinoma is usually several years after the initial diagnosis. Therefore, some authors recommend close, prolonged (preferably life-long) follow-up [2,8].

Magnetic resonance imaging (MRI) may have an advantage in distinguishing SNIPs from SCC. MRI can identify inflammation more clearly, as well as tumor margin, tumor extent, and convoluted cerebriform pattern, which is considered to be a valuable SNIP feature [4]. MRI shows that the cerebriform aspect is related to the invagination found in pathologic examination; its focal or total disappearance suggests synchronous carcinoma [2]. 18FDG-PET/CT can distinguish polyposis, SNIPs, and SCC by distinct maximum standardized uptake value (SUVmax). Higher SNIP SUVmax values may indicate the possibility of an associated malignancy [4]. Preoperative biopsy is an ineffective method of identifying malignant SNIPs, and SNIPs mostly become malignant from the center; therefore, multiple preoperative biopsies should be performed at different locations of the tumor tissue, particularly near the base of the central area of the tumor, to prevent misdiagnosis [5].

At present, the specific mechanisms of SNIP-associated malignancy remain unclear [5]. Tsou., *et al*. indicated that Ki-67 and proliferating cell nuclear antigen interacted with cyclin-dependent kinase 1, which might lead to the malignant transformation of SNIPs [3]. Udager., *et al*. proposed that the activation of epidermal growth factor receptor mutations play an essential role in the pathogenesis of SNIPs and associated SCC [9]. Histologically, the most common malignancy associated with SNIPs is SCC. In recent studies, malignant transformation to SCC has been observed in 11% of SNIPs [2-5]. Compared with pure primary SCC, malignant trans-

formed SCC has a better therapeutic outcome. Complete removal of the tumor, which ensures negative margins and facilitates thorough histological examination, can improve the prognosis of malignant transformed SCC when supplemented with postoperative radiotherapy and chemotherapy [5].

However, increasing evidence demonstrates that a pathologic collision exists between SNIPs and other tumors (esthesioneuroblastoma, nasal-type NK/T-cell lymphoma, angiofibroma, monophasic fibrous synovial sarcoma, and intestinal-type adenocarcinoma) [4,10]. SNIPs accompanied by malignancies other than SCC are extremely rare, which may lead to pretherapeutic misdiagnosis and an increased risk of recurrence. This may be due to the lack of consensus regarding therapeutic regimens, such as the surgical margin, doses and cycles of radiotherapy, and choice of chemotherapy drugs, as well as the lack of evidence-based analysis in large, well-controlled trials [4]. Through an extensive literature search, a single case of the synchronous occurrence of a SNIP and nasal-type NK/T-cell lymphoma was identified [6]. Other than this case, we found no cases that reported nasal-type NK/T-cell lymphoma occurring at the site from which a SNIP was previously resected, as observed in our case.

Nasal-type NK/T-cell lymphoma is characterized as a very aggressive disease with local destructive activity and refractoriness to treatment. It can spread to the central nervous system, skin, and testes, and it can cause hemophagocytosis in the bone marrow. The reported median overall survival of nasal-type NK/T-cell lymphoma is 13 to 38 months [6]. Nasal-type NK/T-cell lymphoma has been reported to be causally associated with the Epstein-Barr virus [6]. Though the presence of EBV has been reported in both NK/T-cell lymphoma and SNIPs, subsequent studies have refuted any association between SNIPs and EBV [1,6]. SNIP-associated nasal-type NK/T-cell lymphoma may pose diagnostic and therapeutic challenges; however, based on our case, blood-tinged nasal discharge could alert the otolaryngologist to the occurrence of SNIP-associated malignancy. Early diagnosis, followed by endoscopic excision and adjuvant CCRT, can provide good treatment results.

Conclusion

SNIPs accompanied by malignancies other than SCC are extremely rare. In summary, this is the first reported case of nasal-type NK/T-cell lymphoma occurring at the site from which a SNIP was previously resected. In addition, we provide our experience of treatment of this rare case. In such cases, awareness and early diagnosis, followed by endoscopic excision and adjuvant CCRT, can provide good treatment results. This report expands the spectrum of reported SNIP-associated malignancy and emphasizes the importance of considering the malignant transformation of SNIPs and close, prolonged (preferably life-long) follow-up.

Disclosure of Conflict of Interest

None.

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