VIA MEDICA

ORIGINAL ARTICLE

Folia Morphol.
Vol. 82, No. 3, pp. 696–703
DOI: 10.5603/FM.a2022.0051

ISSN 0015–5659
eISSN 1644–3284
journals.viamedica.pl

Anatomical identification of supraseptal posterior ethmoid cells and its significance for endoscopic sinus surgery

J. Liu[1], Y. Wang[1], Z. Yan[2], Y. Yang[3]

[1]*Department of Otorhinolaryngology Head and Neck Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing, P.R. China*
[2]*Department of Otorhinolaryngology, Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Beijing, P.R. China*
[3]*Department of Otolaryngology, Beijing Hospital, National Centre of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, P.R. China*

[Received: 10 April 2022; Accepted: 9 May 2022; Early publication date: 20 May 2022]

Background: *To investigate the anatomical imaging characteristics of supraseptal posterior ethmoid cells (SPEC).*
Materials and methods: *Paranasal sinus computed tomography scans of 153 inpatients from February 2019 to September 2021 were reviewed, and the anatomical characteristics of SPEC in the scans were collected.*
Results: *Supraseptal posterior ethmoid cells are posterior ethmoid (PE) cells extending medially and superiorly to the posterior superior of the nasal septum and into the sphenoid body but not close to the optic canal. The SPEC, Onodi cell, and sphenoidal sinus (SS) may appear in the posterior superior of the nasal septum, but the occurrence rate of the SPEC (5.88%; 9/153 cases) was significantly lower than that of the SS (22.88%) and Onodi cell (21.57%). The anterior SPEC is adjacent to the cribriform plate, the perpendicular plate of the ethmoid bone and the posterior ethmoidal artery (PEA). The posterior SPEC is adjacent to the SS and PE (6/9 cases), the SS and Onodi cell (2/9 cases) or the PE only (1/9 cases).*
Conclusions: *The SPEC is a rare pneumatization that occurs in the posterior superior area of the nasal septum. Care should be taken to protect the skull base, cribriform plate and PEA when opening the SPEC during endoscopic sinus surgery.*
(Folia Morphol 2023; 82, 3: 696–703)
Key words: ethmoid sinus, posterior ethmoid cell, sphenoid sinus, anatomic variation, endoscopic sinus surgery, tomography, X-ray computed

INTRODUCTION

Pneumatization of the nasal septum has aroused great interest from scholars in recent years [4, 12, 13, 16]. Pneumatization of the anterior nasal septum mainly originates from the frontal recess and crista galli, then extending to the perpendicular plate of the ethmoid bone (PPE), which is known as the sinus septi nasi [13]. Furthermore, ethmoid cells can expand to the posterior superior of the nasal septum [4, 16].

Address for correspondence: Prof. J. Liu, Department of Otorhinolaryngology Head and Neck Surgery, Beijing Chaoyang Hospital, Capital Medical University; No. 8, Gongti South Road, Chaoyang District, Beijing 100020, China, e-mail: sanming_1978@163.com; Prof. Y. Yang, Department of Otolaryngology, Beijing Hospital, China, e-mail: yangyi2905@bjhmoh.cn

The cell in the posterior nasal septum has been reported and focused on because of the pneumatization observed in the computed tomography (CT) coronal plane that occurs in the superior or middle area of the posterior nasal septum [12, 13]. In fact, the so-called air cell in the middle of the posterior nasal septum is essentially pneumatization of the sphenoid rostrum; it is found on the coronal plane and is not an independent air cell [13]. A similar situation can also occur above the posterior nasal septum, with the sphenoid sinus (SS) extending anteriorly and superiorly on one side; it appears in the coronal plane rather than as an independent air cell. In addition, posterior ethmoid (PE) cells extend to the SS to form the superolateral type (Onodi cell), inferolateral type (Jinfeng cell) and whole lateral type of sphenoethmoidal cells [7, 9]. Some sphenoethmoidal cells can also expand anteriorly and medially, being displayed in the coronal plane [16]. Hence, there are many originations of the cell in the posterior superior of the nasal septum, which need to be carefully identified.

In the present study, the cell we focused on and described is an independent air cell that is formed by pneumatization expansion of the PE cells to the posterior superior of the nasal septum but is not adjacent to the optic canal, which is called a supraseptal posterior ethmoid cell (SPEC). This retrospective analysis of the anatomical features of the SPEC in CT scans is intended to help surgeons open it safely during endoscopic sinus surgery (ESS) because of its important anatomical location [16].

MATERIALS AND METHODS

Study design

We conducted a retrospective analysis of paranasal sinus CT scans obtained from adult inpatients seen in our hospital from February 2019 to September 2021. All of these patients underwent a routine paranasal sinus CT scan because of sinus disease or nasal septum deviation and to confirm the clinical symptoms or determine diagnosis. CT scans were also intended to obtain accurate anatomy before ESS [15].

Each CT scan was performed in the Radiological Department, Beijing Chaoyang Hospital, Capital Medical University. A total of 153 patients were included, and their CT images were reviewed and analysed. Some of these CT data have been used in a previous study [8]. The collection of these CT data was approved by the Ethics Committee of Capital Medical University affiliated with Beijing Chaoyang Hospital. The study was also conducted in accordance with the Helsinki Declaration.

The enrolment criteria were as follows: 1) no history of head or sinus injury; 2) no history of sinonasal surgery or septoplasty; 3) clear PE, nasal septum and SS anatomical structures; and 4) age older than 18 years. Cases were excluded if CT findings of sinonasal disease (e.g., neoplasm, fungal sinusitis, osteofibroma, fibrous dysplasia or chronic rhinosinusitis) involving the PE or SS occurred [9].

CT examination and analysis

The CT scanning range spanned from the superior margin of the frontal sinuses to the inferior margin of the maxillary alveolar process. A GE Lightspeed 64-slice spiral CT (USA) system was used with a bone imaging algorithm. CT scans were obtained at a section thickness of 0.625 mm and an interval of 0.5 mm. The following parameters of acquisition were used: 120 kV, 320 mA, collimation 40 × 0.6 mm, tube rotation 1 s, matrix size 512 × 512, and reconstruction thickness 3 mm [7, 9].

The GE system was used to obtain multiplanar reconstructions using three anatomical planes. The standard plane of coronal reconstruction requires being perpendicular to the hard palate to minimise the effect of the reconstruction plane on the observations (Fig. 1). An indicator line of reconstruction is shown in Figure 1, and this reconstruction was designed to avoid the excessive forward or backward inclination of the reconstruction plane to affect the appearance of the cell on the coronal plane.

GE Centricity Enterprise Web 3 software (GE Medical Systems) was used for viewing and measuring. Continuous observation was performed by sliding the computer mouse. The posterior nasal septum and its adjacent SS and PE were the main structures that were observed.

Identification of the SPEC

Definition of the SPEC. Below the sphenoid planum, the PE was expanded above the posterior nasal septum but was not adjacent to the optic nerve. We referred to this cell as the SPEC (Figs. 2–4).

Determination of the SPEC. On the midsagittal plane, the posterior edge of the hard palate serves as the posterior boundary of the nasal septum. Before the posterior edge, if the PE could be seen at the top of the posterior nasal septum in the coronal

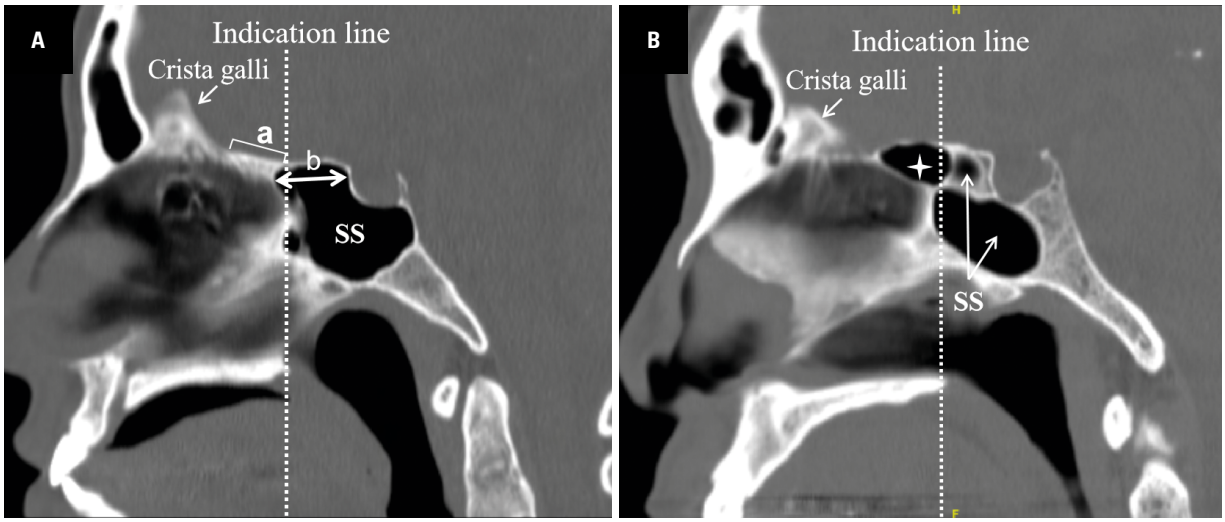

Figure 1. The location line of the coronal reconstruction of the computed tomography scan (the indication line in the midsagittal plane); **A.** The area a is the sphenoid bone under the sphenoid planum, which is a potential area for the pneumatization and expansion of the air cell. Line 'b' indicates the range of the anterior extension of the sphenoidal sinus (SS); **B.** The asterisk refers to the supraseptal posterior ethmoid cells displayed in the midsagittal plane, and this pneumatization position is area 'a' of panel A (panel B were obtained from the patient presented in Figure 2).

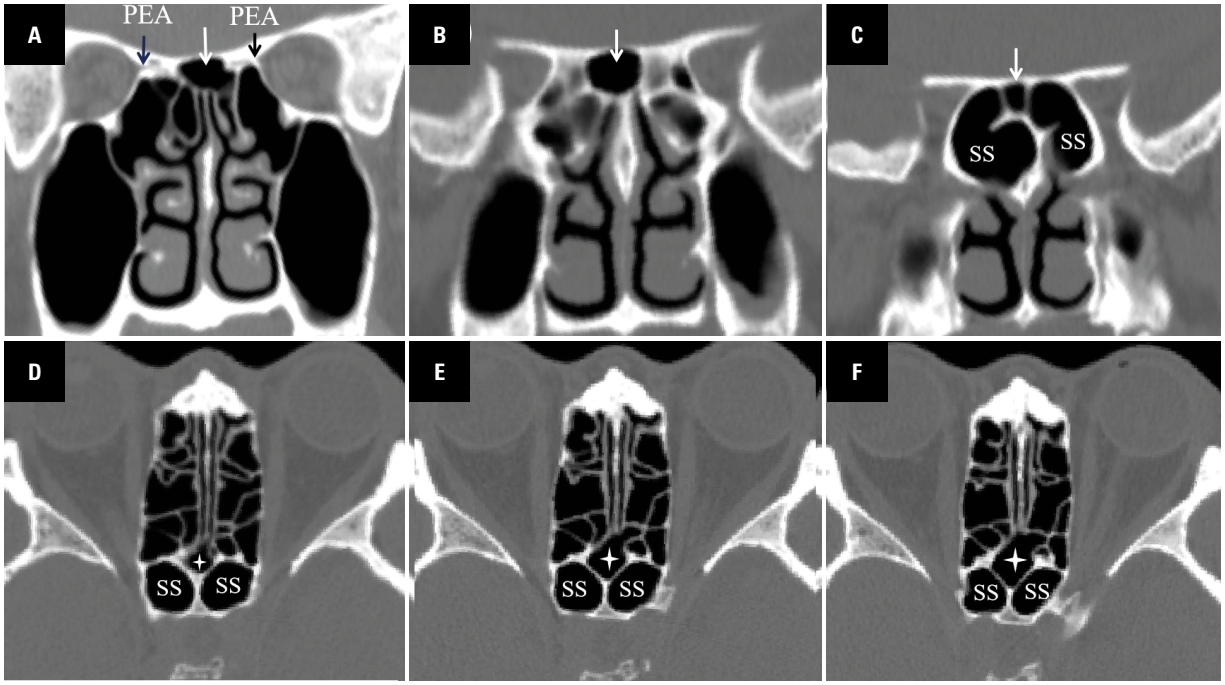

Figure 2. The location of the supraseptal posterior ethmoid cells (SPEC) in the coronal and axial plane of the computed tomography (CT) images. A series of coronal CT scans (**A–C**) showing that a cell (indicated by the arrow) lies to the posterior superior area of the nasal septum. An axial CT scan of the top-down series (**D–F**) showing the SPEC (indicated by the star) located between the two sphenoidal sinus (SS) and the perpendicular plate of the ethmoid bone. The SPEC is connected to the left posterior ethmoid and drains into it; PEA — posterior ethmoidal artery.

plane, this PE was identified as an SPEC (Figs. 2–4). As observed on consecutive sections in all three planes (axial, coronal and sagittal), if the posterior superior cell of the nasal septum was an Onodi cell or/and the SS, it was identified and excluded (Figs. 5–7). SPEC identification was performed by one otolaryngologist (L.J.), and cases of SPEC were confirmed by two otolaryngologists working together (L.J. and W.Y.).

Determination of the Onodi cell

The Onodi cell is the most posterior ethmoid air cell that pneumatizes superolateral, superior, or lat-

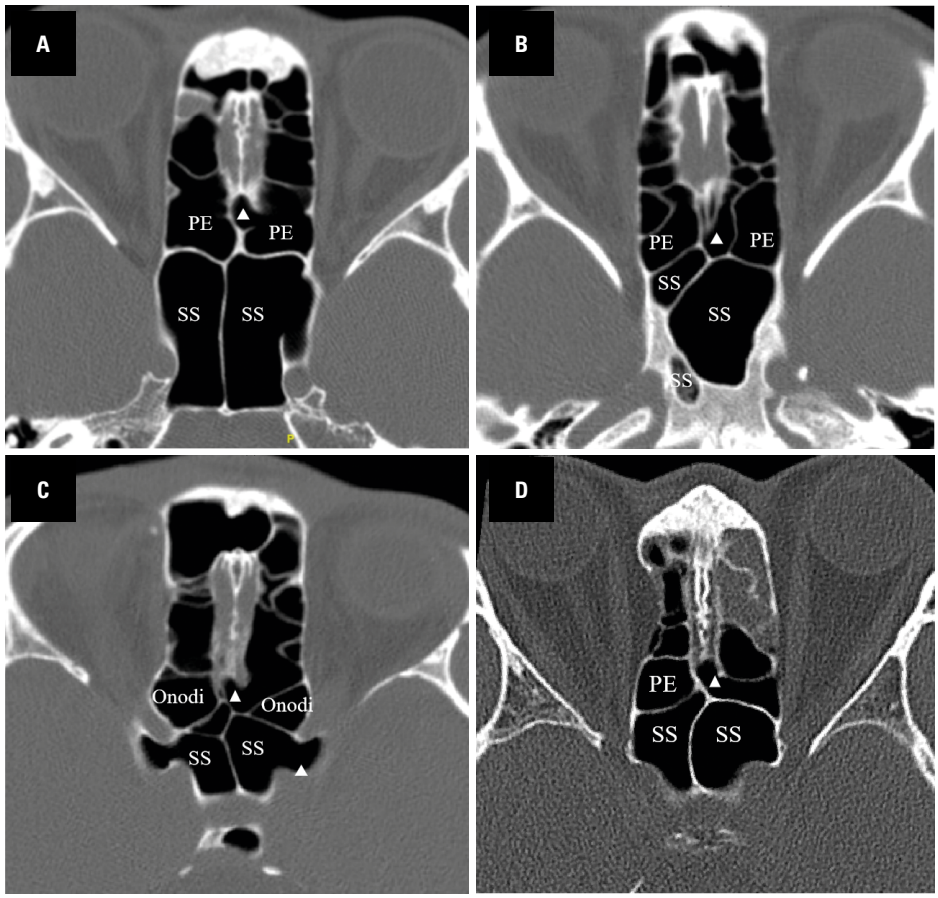

Figure 3. The axial plane of computed tomography scan shows the adjacent structure of the supraseptal posterior ethmoid cells (SPEC) (indicated by the solid triangle). Panel **A** shows the posterior portion of the SPEC adjacent to the posterior ethmoid (PE), panels **B–D** show that the posterior portion of the SPEC is adjacent to the sphenoidal sinus (SS). In addition, the SPEC can be adjacent to the PE or Onodi cell on both sides (**B**, **C**) or on one side (**D**).

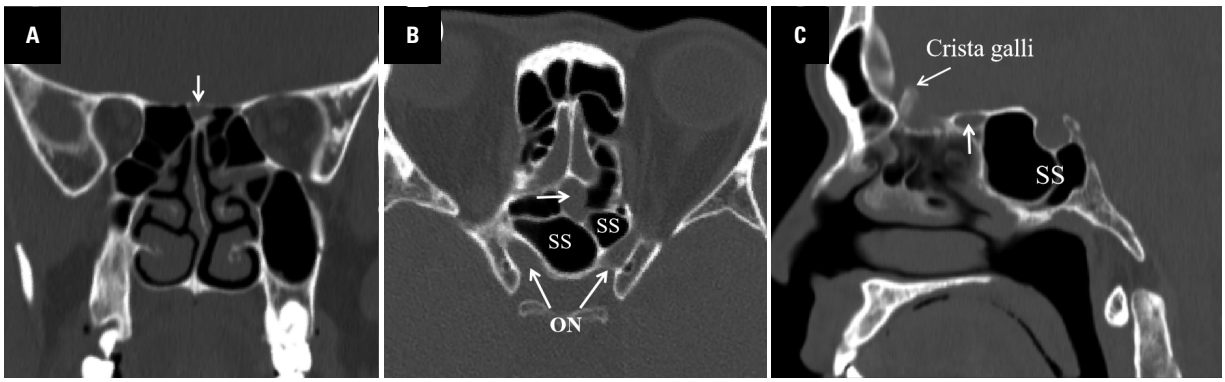

Figure 4. Axial, coronal and sagittal planes (**A**–**C**) show isolated opacities within the supraseptal posterior ethmoid cells (indicated by the arrow); SS — sphenoidal sinus; ON — optic nerve.

eral to the SS and surrounds the optic canal; it penetrates into the anterior clinoid process (Fig. 5) [9, 11].

Statistical analysis

Data regarding patient age are presented as the mean ± standard deviation. Descriptive statistics were determined using SPSS (version 17.0, SPSS, Inc., USA). Incidence rates of the SPEC were calculated to two decimal places. The difference in incidence for the posterior superior cells of the nasal septum (SPEC, Onodi cell and SS) was calculated and evaluated by the chi-squared test. Differenc-

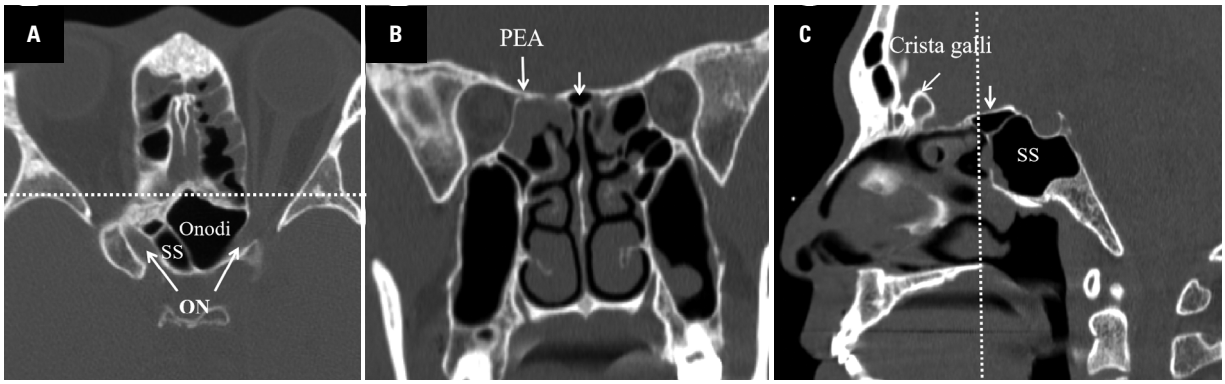

Figure 5. Anterior expansion of the left Onodi cell; panel **A** shows the anterior expansion of the left Onodi cell between the posterior-superior nasal septum and the sphenoid planum. It looks like a supraseptal posterior ethmoid cells in the coronal plane (indicated by the arrow in panels **B** and **C**). The white lines in panels **A** and **C** indicate the reconstruction position in the coronal plane (**B**). In the sagittal plane (**C**), the Onodi cell occupies the entire region under the sphenoid planum at the midline position; PEA — posterior ethmoidal artery; SS — sphenoidal sinus; ON — optic nerve.

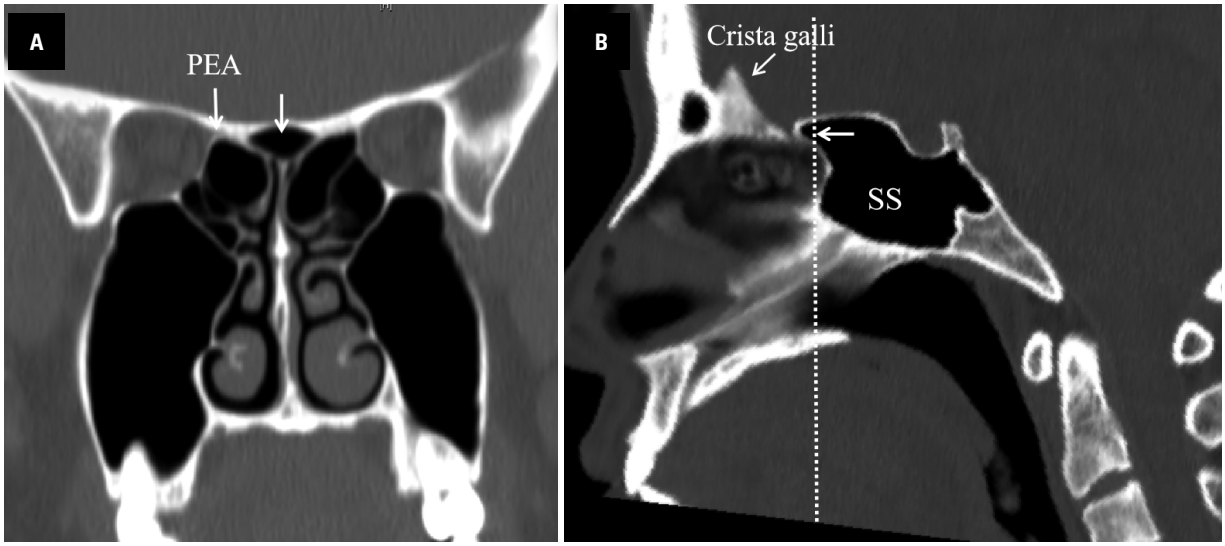

Figure 6. Anterior superior expansion of the sphenoidal sinus (SS). The SS extends anteriorly and superiorly (indicated by the arrow in panels **A** and **B**), filling the entire sphenoid planum (**B**). It looks like a supraseptal posterior ethmoid cells appears in the coronal plane (indicated by the arrow) (**A**); PEA — posterior ethmoidal artery.

es with a $p < 0.05$ were accepted as statistically significant.

RESULTS

General characteristics of the SPEC

The paranasal sinus CT images of 153 patients ranging in age from 18 to 80 years (mean 42.53 ± ± 13.51 years) were reviewed and analysed. Of them, 102 were males and 51 females. If the origination of air cells was not distinguished, the air cells could be seen in the posterior superior of the nasal septum in 50.33% of the patients (77/153 cases) on the coronal plane CT scan. However, most of the posterior superior cells of the nasal septum that were displayed on the coronal plane originated from the anterior and superior pneumatization of the Onodi cell (21.57%; 33/153 cases) and the SS (22.88%; 35/153 cases) under the sphenoid planum. The occurrence rates of the SS and Onodi cell were significantly higher than those of the SPEC (5.88%, 9/153 cases) ($\chi^2 = = 15.896$; $p = 0.000$; $\chi^2 = 17.944$; $p = 0.000$) (Table 1). The SPEC observed originated from the left PE (Figs. 2–4). The incidence of the SPEC in females was 7.84% (4/51 cases), slightly higher than that in males (4.90%, 5/102 cases), though the difference was not significant ($\chi^2 = 0.133$; $p = 0.716$).

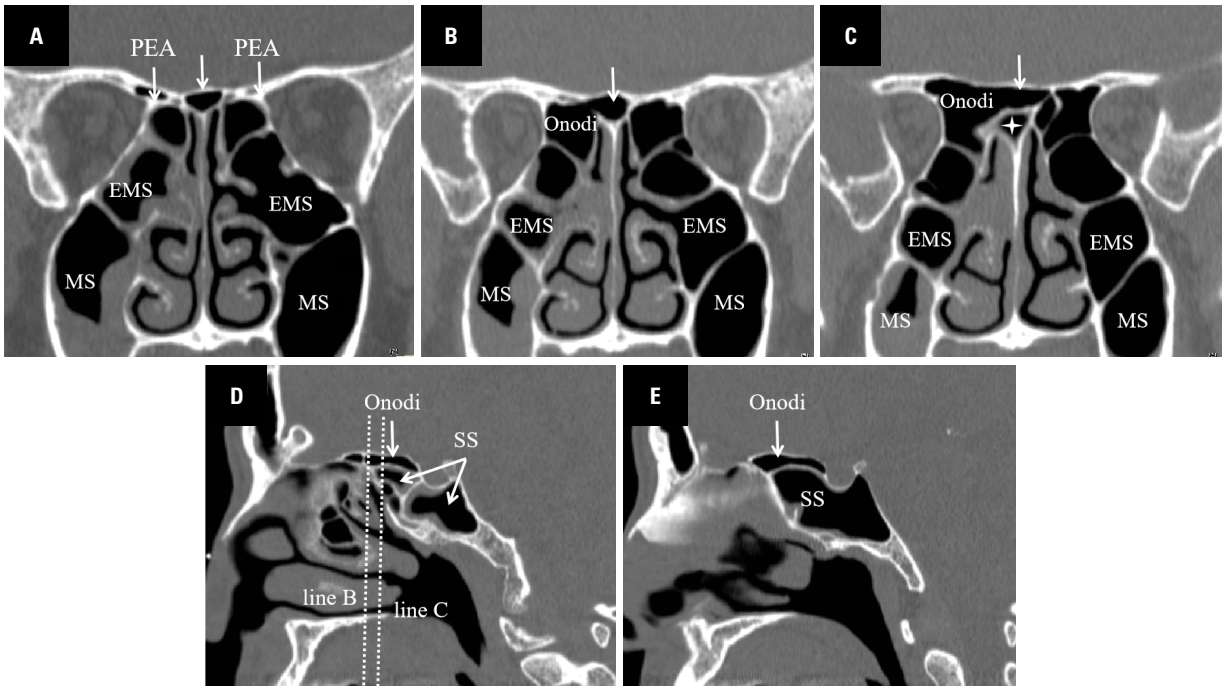

Figure 7. Anterior expansion of the Onodi cell and sphenoidal sinus (SS) simultaneously. A series of coronal computed tomography scans show that a rare variant, the Onodi cell (**A**–**C**), is above the SS (indicated by star); both cells extend to the posterior-superior nasal septum simultaneously (**D**, **E**). Two cells from two different sources appear in the coronal plane and look like supraseptal posterior ethmoid cells (**C**). The two lines in panel **D** indicate the section reconstruction position in the coronal plane (**B**, **C**); EMS — ethmomaxillary sinus; MS — maxillary sinus; PEA — posterior ethmoidal artery.

Table 1. Characteristics of the supraseptal posterior ethmoid cells (SPEC) and differences from the Onodi cell and sphenoidal sinus (SS)

Type	Characteristics	Incidence			
		N	Right	Left	Total sides (%)
SPEC	The cell is limited to the central position under the sphenoid planum and is not close to the optic canal	153	0	9	9 (5.88%)
Onodi cell	The cell extends superolateral to the SS and is attached to the optic canal	153	16	17	33 (21.57%)
SS	The cell is connected to the SS	153	18	17	35 (22.88%)

Imaging anatomy of the SPEC

The SPEC is defined when the PE extends medially and superiorly to the posterior superior of the nasal septum but does not further extend to the SS. Therefore, the SPEC only forms an air cell in the centre of the sphenoid planum (Figs. 2–4). The SPEC is located below the sphenoid planum and is the highest cell at the anterior skull base, slightly higher than the cribriform plate.

The midsagittal plane shows that the SPEC is not pneumatization of the PPE but is due to expansion of the PE in the sphenoid body (Figs. 1B, 2, 4). Therefore, the SPEC is not limited by the nasal septum, and it reaches and crosses the midline (Fig. 2). However, the anterior SPEC is adjacent to the cribriform plate and the upper part of the PPE, and the anterior expansion of the SPEC is limited by the PPE. Inferior expansion of the SPEC is also limited by the sphenoid bone.

Cells on the posterior and surrounding regions of the SPEC show large variation. The SPEC can be adjacent to the SS and PE (6/9 cases), the SS and Onodi cell (2/9 cases) or the PE only (1/9 cases) (Figs. 2–4). The SPEC is not close to the optic canal and can be distinguished from the Onodi cell (Fig. 3).

The SPEC is relatively small. In the midsagittal position, the range of the anterior posterior diameter was between 3.59–14.62 mm (8.60 ± 3.15 mm), and the height was between 2.72–14.36 mm (6.44 ± ± 3.53 mm).

Differences among the SPEC, Onodi cell and SS

The Onodi cell extends to one side of the SS and close to the ipsilateral optic canal. When the Onodi cell extends anteriorly, it will be displayed on the coronal plane, similar to the SPEC (Fig. 5). The SS can extend anteriorly and superiorly, which is also similar to the SPEC (Fig. 6), but it is easy to distinguish from the SPEC (Table 1). Interestingly, in a few cases, the Onodi cell and SS extended to the middle line together, with stacking of the cells at the middle line. In such cases, the Onodi cell was above, and the SS was below (Fig. 7).

The relationship between the SPEC and the posterior ethmoidal artery

The anterior SPEC is adjacent to the posterior ethmoidal artery (PEA) on both sides (Fig. 2). Even when the Onodi cell or SS extended forward and was displayed in the posterior superior of the nasal septum on the coronal plane, the anterior of the cell was also adjacent to the PEA (Figs. 5–7).

DISCUSSION

At present, the cell is described and named SPEC because it is a medially and superiorly extended PE that is located the posterior superior of the nasal septum between the SS/PE and the PPE. This air cell is also called the supraseptal ethmoid sinus cell, sphenoseptal cell or ethmoidal origin of nasal roof pneumatization [4, 14, 16]. Nevertheless, the meaning of "supraseptal ethmoid sinus cell" and "sphenoseptal cell" does not accurately describe the fact that this cell originates from the PE [4, 16]. Therefore, the present study adopts the name supraseptal posterior ethmoid cell — SPEC.

Initially, the SPEC was a focus owing to the pneumatization seen in the posterior superior of the nasal septum on the coronal plane [5, 13]. In fact, identification of the SPEC must be made using combined imaging from the sagittal and axial planes; indeed, there would be many erroneous judgments if the SPEC was confirmed based only on coronal plane observations [14]. Anterior-superior expansion of the SS and sphenoethmoidal cell can also appear in the posterior superior of the nasal septum on the coronal plane (Figs. 5–7). The present results show that anterior expansion of the Onodi cell (21.57%) and the SS (22.88%) is significantly more common than the SPEC (5.88%) ($p < 0.05$). Therefore, we should pay attention to distinguishing the SPEC from the Onodi cell and SS (Table 1).

Based on the present observation, the nature of the SPEC is that the PE extends medially and superiorly along the sphenoid planum to the posterior superior of the nasal septum. The SPEC is still in the sphenoid bone, but it does not further pneumatize to the SS and is not close to the optic canal, which is different from the Onodi cell [9, 11]. The SPEC, as a type of outward expansion of the PE, reflects the extreme variation characteristics of the PE [3, 9, 10]. Similar to previous reports, the PE extends from the superior, superolateral, lateral, inferolateral areas of the SS into the sphenoid bone to form the Onodi cell, Jinfeng cell and central Onodi cell [1, 7, 9]. In addition, as the PE extends to the orbital roof and maxillary sinus [6, 18], it is not surprising that PE extends to the posterior superior of the nasal septum. Sex differences in the morphology of the craniofacial bone and paranasal sinus have also been reported [2, 17]. However, according to the present results, the SPEC incidence in females (7.84%) was slightly higher than that in males (4.90%), even though the difference was not significant [16].

The SPEC is located outside of the conventional area of ethmoidal cells, which is easy to ignore during ESS. Therefore, we should recognize the possibility of isolated PE appearance in the central area under the sphenoid planum (5.88%) when reviewing CT before ESS. Furthermore, the presence of the SPEC may increase ESS difficulty and surgical risk [4, 14]. The SPEC shows a small space and narrow drainage channels, and the anterior and superior regions of the SPEC are adjacent to the skull base, cribriform plate and PPE. In the event that an SPEC appears and there are lesions or opacities in it (Fig. 4), the SPEC should be opened inferiorly and posteriorly to avoid injury to the skull base and to allow adequate opening, which can also avoid residual lesions or poor drainage during ESS [4, 14].

Moreover, the SPEC and Onodi cell can appear simultaneously (2/9 cases), which should be carefully identified to avoid a missed SPEC and insufficient surgery [16]. The SPEC is the highest ethmoidal cell and is close to the skull base. The roof of the SPEC is the sphenoid planum and can be used as a marker of the skull base. Overall, precise identification and localization of the SPEC during surgery is very important. Moreover, our observations show that the SPEC is located behind the PEA; thus, when opening the SPEC during ESS, we should pay attention to avoid damage to the PEA. Even when the Onodi cell or the

SS extends forward and is displayed in the posterior superior of the nasal septum on the coronal plane, the anterior area of the cell is adjacent to the PEA (Figs. 4, 5).

CONCLUSIONS

The SPEC is a rare variation; it is the PE cells extending medially and superiorly to the posterior superior nasal septum and into the sphenoid body but not close to the optic canal. The anterior SPEC is adjacent to the cribriform plate, PPE and PEA. Care should be taken to protect the skull base, cribriform plate and PEA when opening the SPEC during ESS.

Funding

This work was partially supported by a grant Research and Transformation application of Capital Clinical Characteristic Diagnosis and Treatment Technology from Beijing Municipal Science and Technology Commission (Z211100002921022).

Conflict of interest: None declared

REFERENCES

1. Cherla DV, Tomovic S, Liu JK, et al. The central Onodi cell: A previously unreported anatomic variation. Allergy Rhinol (Providence). 2013; 4(1): e49–e51, doi: 10.2500/ar.2013.4.0047, indexed in Pubmed: 23772328.
2. Demiralp KO, Kursun Cakmak S, Aksoy S, et al. Assessment of paranasal sinus parameters according to ancient skulls' gender and age by using cone-beam computed tomography. Folia Morphol. 2019; 78(2): 344–350, doi: 10.5603/FM.a2018.0089, indexed in Pubmed: 30280374.
3. Gibelli D, Cellina M, Gibelli S, et al. Anatomical variants of ethmoid bone on multidetector CT. Surg Radiol Anat. 2018; 40(11): 1301–1311, doi: 10.1007/s00276-018-2057-6, indexed in Pubmed: 29934677.
4. Gore MR. The supraseptal ethmoid sinus cell: A previously unreported ethmoid sinus variant. Clin Case Rep. 2019; 7(7): 1306–1308, doi: 10.1002/ccr3.2215, indexed in Pubmed: 31360472.
5. Huang D, Li W, Gao L, et al. Study on computed tomography features of nasal septum cellule and its clinical significance. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2008 ; 22(5): 217–219, indexed in Pubmed: 18476611.
6. Liu J, Dai J, Wen X, et al. Imaging and anatomical features of ethmomaxillary sinus and its differentiation from surrounding air cells. Surg Radiol Anat. 2018; 40(2): 207–215, doi: 10.1007/s00276-018-1974-8, indexed in Pubmed: 29368251.
7. Liu J, Liu Q, Wang N. Posterior ethmoid cell expansion towards the inferolateral region of the sphenoid sinus: a computed tomography study. Surg Radiol Anat. 2019; 41(9): 1011–1018, doi: 10.1007/s00276-019-02277-w, indexed in Pubmed: 31250138.
8. Liu J, Qian Z, Yan Z, et al. Asymmetry of inferior turbinate in patients with nasal septum deviation and its significance for nasal ventilation surgery. Eur Arch Otorhinolaryngol. 2022; 279(5): 2423–2431, doi: 10.1007/s00405-021-07012-z, indexed in Pubmed: 34302496.
9. Liu J, Yuan J, Dai J, et al. The Whole Lateral Type of the Sphenoethmoidal Cell and Its Relevance to Endoscopic Sinus Surgery. Ear Nose Throat J. 2021; 100(9): NP416––NP423, doi: 10.1177/0145561320922119, indexed in Pubmed: 32396389.
10. Márquez S, Tessema B, Clement PAr, et al. Development of the ethmoid sinus and extramural migration: the anatomical basis of this paranasal sinus. Anat Rec (Hoboken). 2008; 291(11): 1535–1553, doi: 10.1002/ar.20775, indexed in Pubmed: 18951481.
11. Meloni F, Mini R, Rovasio S, et al. Anatomic variations of surgical importance in ethmoid labyrinth and sphenoid sinus. A study of radiological anatomy. Surg Radiol Anat. 1992; 14(1): 65–70, doi: 10.1007/BF01628046, indexed in Pubmed: 1589850.
12. Mladina R, Antunović R, Cingi C, et al. Sinus septi nasi: anatomical study. Clin Anat. 2017; 30(3): 312–317, doi: 10.1002/ca.22850, indexed in Pubmed: 28192871.
13. Mureşan AN, Mogoantă CA, Stănescu R, et al. The sinus septi nasi and other minor pneumatizations of the nasal septum. Rom J Morphol Embryol. 2021; 62(1): 227–231, doi: 10.47162/RJME.62.1.22, indexed in Pubmed: 34609425.
14. Mureșan AN, Rusu MC, Rădoi PM, et al. Patterns of pneumatization of the posterior nasal roof. Tomography. 2022; 8(1): 316–328, doi: 10.3390/tomography8010026, indexed in Pubmed: 35202191.
15. Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinology. Rhinology. 2019; 57(Suppl S28): 1–41, doi: 10.4193/Rhin19.410, indexed in Pubmed: 31376816.
16. Saka C, Öcal B, Çadallı Tatar E, et al. How important is the sphenoseptal cell in identifying the skull base? Recent incidence and demonstration of endoscopic surgical steps. Turk J Med Sci. 2021; 51(4): 1889–1893, doi: 10.3906/sag-2012-187, indexed in Pubmed: 33862672.
17. Tomaszewska IM, Frączek P, Gomulska M, et al. Sex determination based on the analysis of a contemporary Polish population's palatine bones: a computed tomography study of 1,200 patients. Folia Morphol. 2014; 73(4): 462–468, doi: 10.5603/FM.2014.0069, indexed in Pubmed: 25448904.
18. Zhou J, Xie Y, Huang Xi, et al. The supraethmoidal roof cell: an unreported sinus anatomic variation. OTO Open. 2021; 5(2): 2473974X211022318, doi: 10.1177/2473974X211022318, indexed in Pubmed: 34164594.