Abstract

Basaloid squamous cell carcinoma (BSCC), a histologically distinctive variant of squamous cell carcinoma comprising basal cell carcinoma and squamous cell carcinoma, is aggressive and shows a poor prognosis because of frequent lymph node invasion and distant metastases. To date few articles regarding chemotherapy for metastatic disease have been reported, thus feasible chemotherapy is not well established. Cetuximab is a monoclonal antibody for epithelial growth factor receptor (EGFR), which has great efficacy for head and neck squamous cell carcinoma due to EGFR signaling pathway blockage. Because BSCC also highly expresses EGFR, cetuximab may be effective for BSCC. We report here a first case of recurrent BSCC in the ethmoid sinus with intracranial extension treated with cetuximab-based chemotherapy, which revealed great response in a 40-year-old man. Positron emission tomography (PET) revealed no lymph node or distant metastasis. The patient underwent chemoradiotherapy 66 Gy in 33 fractions with triweekly 100 mg/m^2 cisplatin. However, 12 weeks after treatment completion PET revealed a residual tumor at the primary cancer site. Combination therapy with weekly paclitaxel and cetuximab was started, and complete response was observed 2 months from treatment initiation. The patient has maintained complete response for 32 months, and no tumor regrowth has been observed.

Key words: Basaloid squamous cell carcinoma, cetuximab, head and neck, metastasis, chemotherapy

Introduction

Basaloid squamous cell carcinoma (BSCC) is a histologically distinctive variant of squamous cell carcinoma comprising 2 parts: basal cell carcinoma and squamous cell carcinoma [1]. BSCC is uncommonly found in the head and neck region, and in the nasal cavity is especially rare; only 19 cases have been reported in the English literature [2, 3]. BSCC is aggressive and shows a poor prognosis because of frequent lymph node invasion and distant metastases, however only article regarding the treatment for recurrent and metastatic (RM) BSCC was found in the literature [4]. This reported a metastatic esophageal BSCC case treated with combination cisplatin and 5-fluorouracil. Therefore, the treatment for RM-BSCC has not been well established, especially in head and neck region.

Cetuximab is recombinant human/mouse chimeric epidermal growth factor receptor (EGFR) monoclonal antibody. Over 90% of head and neck squamous cell carcinoma (HNSCC) express high levels of EGFR, and cetuximab enhances antitumor effect for HNSCC in combination therapy with cytotoxic agents [5]. BSCC in the head and neck region also highly expresses EGFR, which means that cetuximab may be also effective for BSCC [6].

Case

A 40-year-old man was unexpectedly diagnosed with a tumor in the left ethmoid sinus upon examination of a head injury with computed tomography (CT). The patient was referred to our hospital for further examination and treatment. On endoscopic examination, a tumor was observed at the left middle meatus. A biopsy was performed, and the microscopic findings with hematoxylin and eosin staining revealed peripheral palisade of atypical cells that comprised a differentiated squamous cell carcinoma, which was histologically diagnosed as BSCC (Fig. 1A, B). Immunohistochemical staining for EGFR was performed, and EGFR over expression was observed on the cell membrane of the

carcinoma (Fig. 1C). Magnetic resonance imaging (MRI) with contrast effect revealed left ethmoid sinus tumor involved dura via anterior skull base, and intraorbital invasion (Fig. 2A,B). Positron emission tomography (PET) revealed neither lymph node nor distant metastatic disease. The patient was diagnosed as BSCC in the left ethmoid sinus cT4bN0M0 Stage IVB, and underwent concurrent chemoradiotherapy 66 Gy in 33 fractions with triweekly 100 mg/m^2 cisplatin.

Definitive treatment has been completed with no treatment delay, and 3 cycles of cisplatin at a total dose of 300 mg/m^2 was administrated concurrently with radiotherapy. However, adequate response was not observed, and MRI at 4 weeks after treatment completion revealed a residual tumor at primary cancer site (Fig. 3A). PET 12 weeks post treatment completion also revealed residual tumor at the left ethmoid sinus and dura (Fig. 3B). The patient refused to undergo salvage surgery and surgical biopsy for residual tumor. Thus, a combination therapy of cetuximab and paclitaxel was selected for the treatment of residual disease because the patient was refractory to platinum-based chemotherapy. Cetuximab was administered at an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. Paclitaxel was administered weekly at a dose of 80 mg/m^2. Combination chemotherapy showed great efficacy on the residual primary cancer, and CT at 2 months post treatment initiation revealed complete response (Fig. 4A). As per the patient's will, chemotherapy was discontinued at 11 months after treatment initiation; therefore, results were observed using only the scan performed. Response of the chemotherapy continued for >21 months from treatment discontinuation, and the patient was free from tumor regrowth (Fig. 4B). Grade2 acneiform dermatitis and paronychia were observed as adverse events of chemotherapy, however both were manageable by using humectants, topical steroids, and addition of minocycline. Hypomagnesemia and any hematologic toxicity have not been observed during chemotherapy.

Discussion

BSCC is a histologically distinctive variant of squamous cell carcinoma composed of 2 parts: basal cell carcinoma and squamous cell carcinoma [1]. BSCC is aggressive and shows a poor prognosis because of frequent lymph node invasion and distant metastases, thus a combination of multimodal therapies may be recommended to improve its prognosis [2]. The effectiveness of concurrent chemoradiotherapy with triweekly cisplatin at a dose of 100 mg/m^2 for locally advanced BSCC has been reported, which means that cisplatin may be just as effective for BSCC as it is for SCC [7]. However only one article was found in the literature regarding treatment for RM-BSCC, which reported great efficacy of combination cisplatin and 5-fluorouracil for metastatic esophageal BSCC [4]. Therefore, the treatment for RM-BSCC, especially arising in head and neck region, has not been well established. In this case, we did not use cisplatin and 5-fluorouracil because of the patient was refractory to chemoradiotherapy with cisplatin; therefore, another treatment option was required. Cetuximab is recombinant human/mouse chimeric EGFR monoclonal antibody. Over 90% of HNSCC express high levels of EGFR, and cetuximab enhances antitumor effect for HNSCC in combination therapy with cytotoxic agents [5]. The combination of cetuximab and weekly paclitaxel could be a treatment option for RM-HNSCC that was refractory to platinum-based chemotherapy. There have been single-arm phase 2 trials of this regimen for RM-HNSCC, and these trials have shown good response rates and survival times [8-10]. Another study has reported that the combination of cetuximab and weekly paclitaxel could be a better treatment option than the 3-drug (cetuximab, cisplatin and 5-fluorouracil) EXTREME combination regimen in selected RM-HNSCC patients [11]. BSCC in the head and neck region highly expressed EGFR, which means that cetuximab may be also effective for BSCC [6]. However, to the best of our knowledge, there have been no case reports and clinical trials targeting EGFR especially using cetuximab in patients with BSCC. In this report, immunohistochemical staining for EGFR of the biopsy specimen confirmed overexpression of EGFR. Furthermore, the patient underwent the combination of cetuximab and

weekly paclitaxel, which revealed great response. Treatment response reached complete response 2 months after treatment initiation, and has continued over 21 months without tumor regrowth from treatment discontinuation. This was a first novel report of cetuximab-based chemotherapy for RM-BSCC in the head and neck region demonstrating good efficacy.

An important limitation of examining EGFR levels using immunohistochemistry is that it does not always predicted anti-tumor effect. There are several reports on resistance to EGFR inhibition, cyclin D1overexpression [12], ErbB2, ErbB3 signaling [13], and EMT [14] associated with resistance. These resistance mechanisms may not be relevant to the present case; however. a good response was obtained. Paclitaxel is an effective treatment not only for RM-HNSCC but also for recurrent and metastatic basal cell carcinoma arising in the skin [15]. Paclitaxel might also be relevant for a good response in our case.

Major adverse events of cetuximab are acneiform rash, paronychia, and dry skin, most of which are manageable by using humectants and topical steroids. Multiple trials have shown the severity of rash was associated with improved survival [16, 17]. Therefore, the management of acneiform rash is very important. It is recommended that severe rash should be treated with tetracyclines, such as minocycline [18]. In our case, adverse events due to combination chemotherapy were Grade2 acneiform rash and paronychia. Acneiform rash might be associated with a good outcome in BSCC just as it was previously reported in SCC. Both adverse events were manageable by using humectants, topical steroids, and addition of minocycline.

Conclusion

We report the first case of RM-BSCC treated with the combination of cetuximab and weekly paclitaxel. Cetuximab-based combination chemotherapy showed novel efficacy for RM-BSCC in the

head and neck region. Adverse events were manageable by using humectants, topical steroids, and addition of minocycline.

Acknowledgment

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Ethical Declaration

The protocol of the investigation has been approved by the Institutional Review Board of Tottori University Hospital (No.19A131).

Conflict of interest

We have no conflicts of interest to report in this case report.

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Figure 1 Pathologic findings

A) Microscopic findings with hematoxylin and eosin (HE) staining revealed peripheral palisade of atypical cells.

B) Cells with hyperchromatic nuclei showed cribriform growth pattern, which means comprised differentiated squamous cell carcinoma.

Figure 2 Intraoperative findings in the left nasal cavity

C) IHC with EGFR: EGFR was positively stained on the cell membrane in the greater part of malignant cells, both squamous cell carcinoma region and basal cell-like carcinoma region.

Figure 2 MRI images in an initial diagnosis

A) Coronal image showed tumor arising in left ethmoid sinus invaded the orbital cavity and infiltrated the frontal skull base.

B) Sagittal image showed tumor infiltrated into skull and dura.

Figure 3 Radiologic findings after the definitive treatment

A) MRI finding at 4 weeks after completion of definitive chemoradiotherapy revealed residual tumor at left ethmoid sinus, frontal sinus, and dura.

B) PET image at 12 weeks after completion of definitive treatment revealed the residual tumor in left ethmoid sinus with high positron emission.

Figure 4 Radiologic findings after combination therapy with cetuximab and paclitaxel

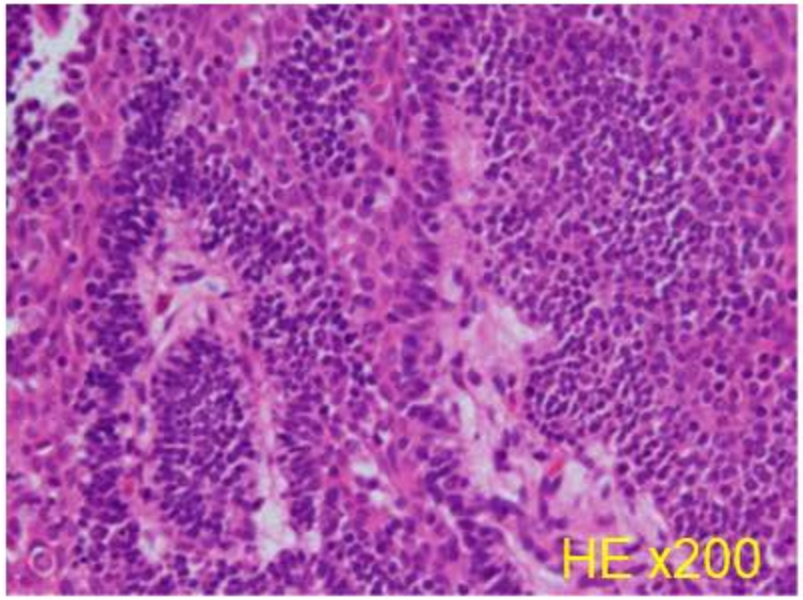
A) Two months after the initiation of chemotherapy, CT with contrast effect revealed the evaluable tumor had completely disappeared.

B) Coronal view of CT with contrast effect revealed that chemotherapy response continued for 21 months after the discontinuation of chemotherapy (32 months from chemotherapy initiation), and the

patient was free from tumor regrowth.

Figure1

A



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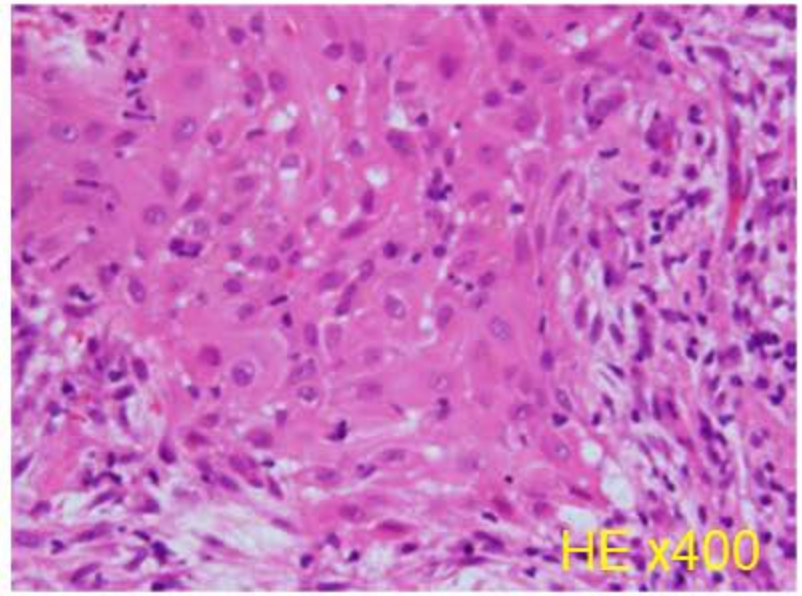

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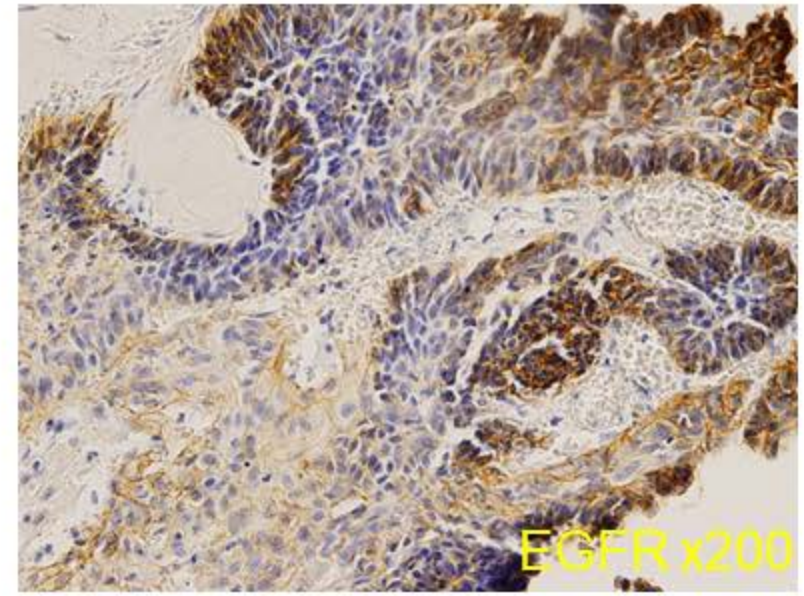
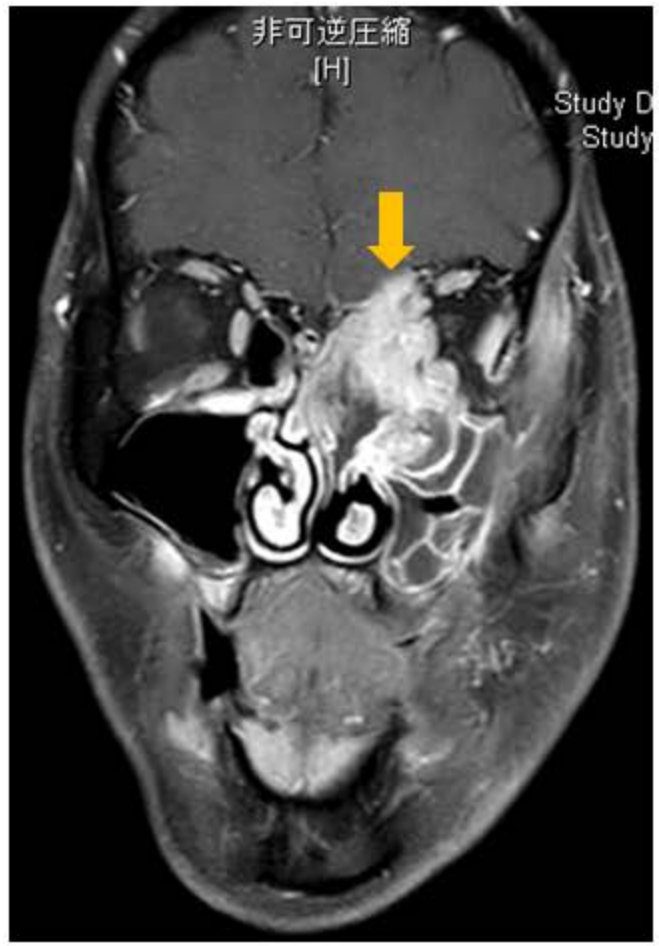


Figure 2

A



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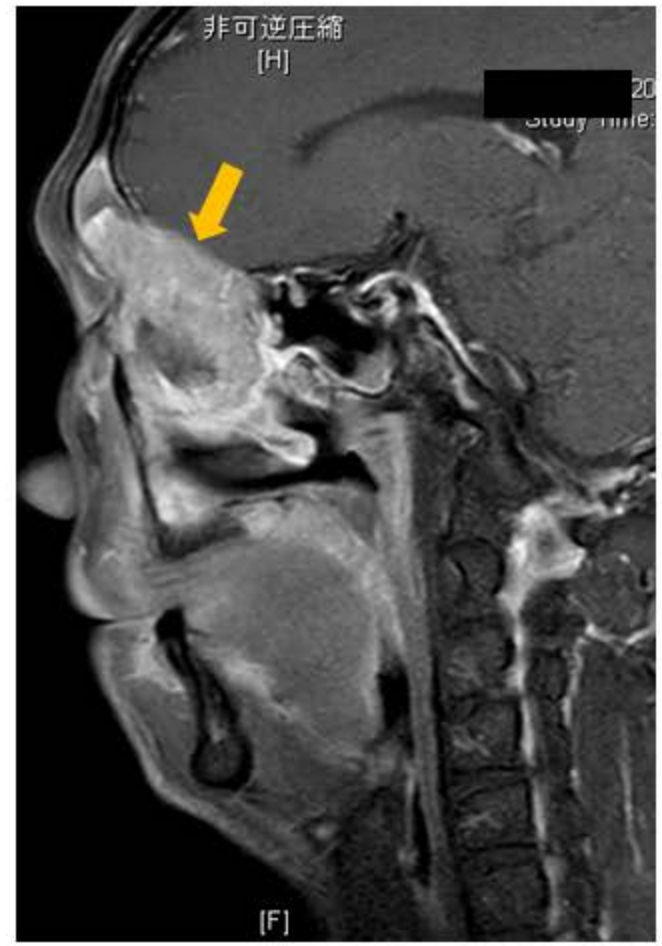

Figure 3

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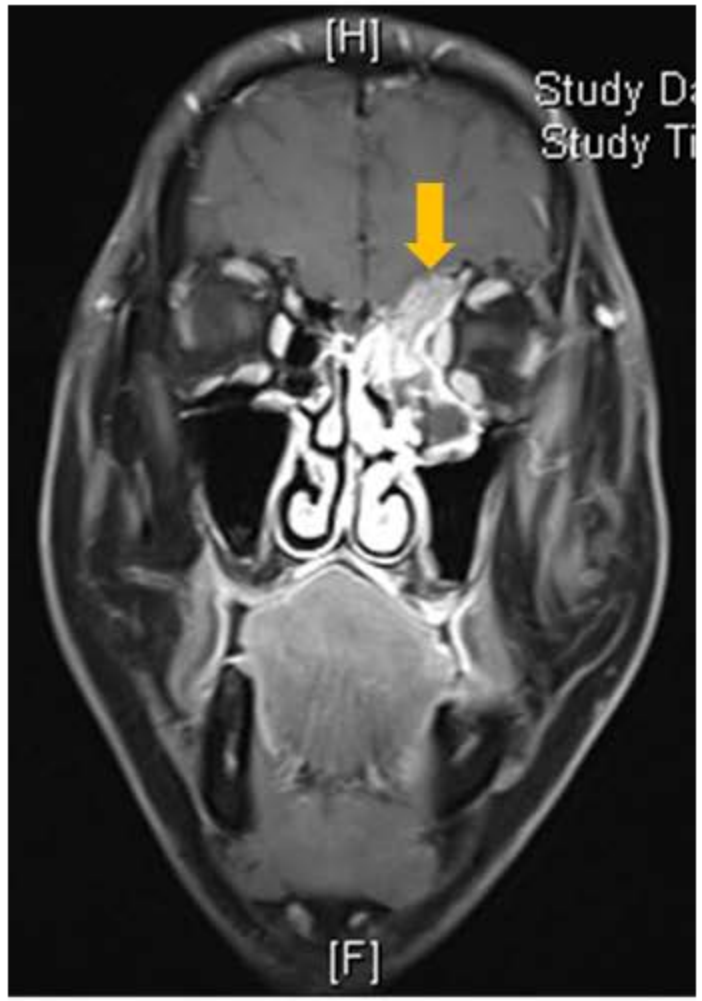

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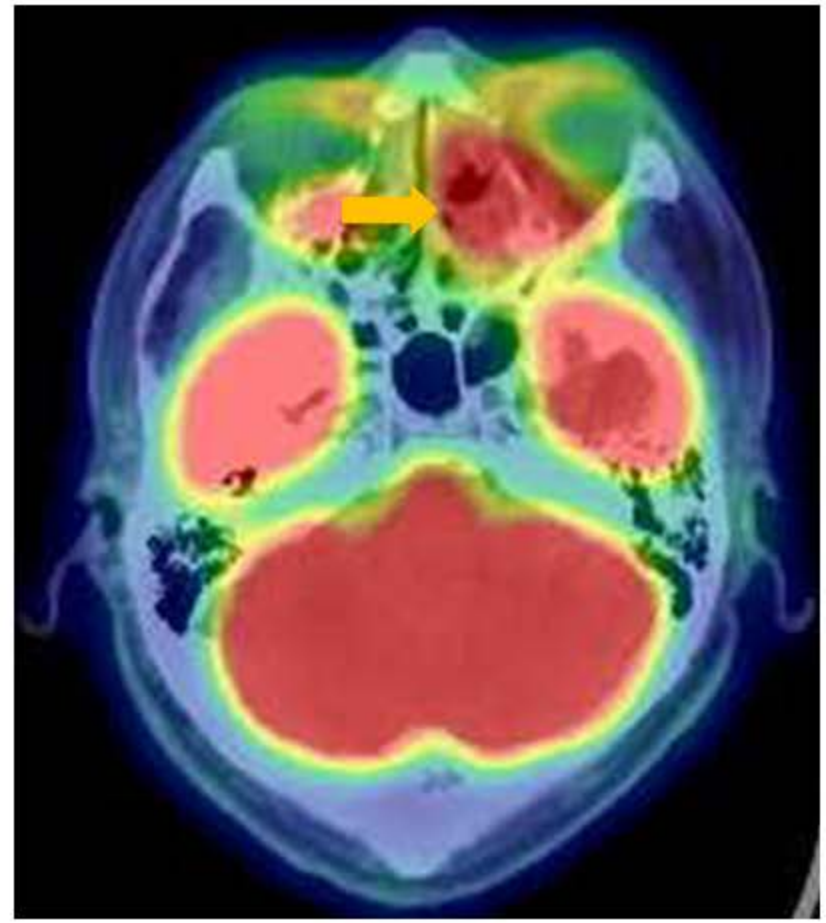

Figure 4

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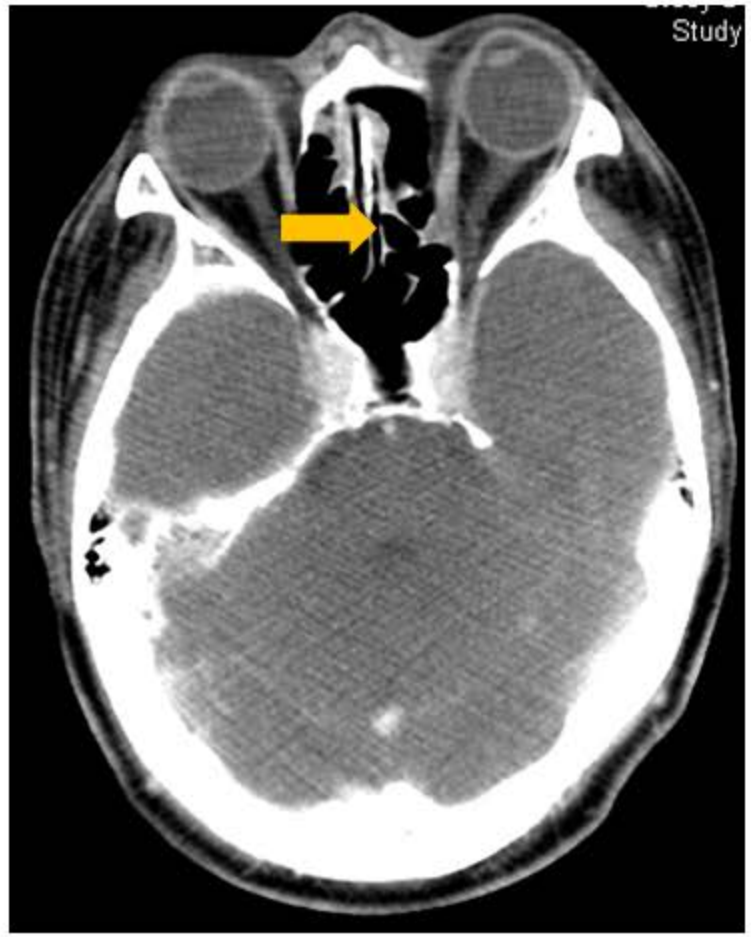

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