



# RADIOLOGICAL SPECTRUM OF SINONASAL MUCORMYCOSIS IN COVID POSITIVE PATIENTS

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**Declarations of interest: none**

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## Abstract

**Rationale and Objectives** - At present, sinonasal mucormycosis is most worrisome COVID-19 related complication in India while western countries have relatively stayed aloof. But given the pervasive nature of fungi and presence of all predisposing conditions even in western countries, it is imperative to have knowledge about the imaging patterns and staging of the disease. In this study, we try to single out factors responsible for the sudden increment in the incidence of sinonasal mucormycosis among covid-19 patients and discuss their imaging features.

**Patients and Methods** - The case records of 30 patients, between January to May, 2021, with positive RT-PCR for COVID-19 and biopsy proven sinonasal mucormycosis were retrospectively evaluated.

**Results** – Out of 30 patients, 28 had raised random blood glucose level and 24 had raised ferritin level. On imaging, nasal cavity involvement was seen in 18 patients. Paranasal sinuses were involved in 28 patients. The disease process also showed involvement of orbit, neck spaces and intracranial extension. We divided sinonasal mucormycosis into four groups and mortality was seen in patients of stage 3 and 4 (total mortality was 26.7%).

**Conclusion** - MRI played an important role in diagnosis and staging of sinonasal mucormycosis as well as determining the extrasinus extent of disease. Mortality was seen in patients presenting in advanced stage of the disease, with orbital or intracranial extension. Thus, it is imperative that high index of suspicion, early imaging with diagnosis and aggressive management protocol needed to reduce morbidity and mortality.

**Keywords:** sinonasal mucormycosis, COVID-19, MRI, staging, risk factors, orbit



## 1. Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Covid-19 (coronavirus disease of 2019) which had started from Wuhan, China in 2019 has now plagued the whole world, and is still a raging pandemic tormenting the globe. Along with, the atrocities of Covid-19 came along a series of collateral complications. The most dreaded among them, at present in India, is sinonasal mucormycosis. India has reported approximately 15,000 cases of sinonasal mucormycosis (SNM) associated with Covid-19 till May, 2021 [1]. At present, SNM has caused havoc in India while western countries have relatively stayed aloof barring few case reports. But given the pervasive nature of fungi and presence of all predisposing conditions even in western countries, it is imperative to study and have knowledge about the imaging patterns and staging of the disease.

SNM is life threatening fungal disease which belong to (Table1) [2, 3]:

SNM is an aggressive disease with a very high morbidity and mortality rate (ranging from 50-85%) [4, 5]. Thus, the outcome of the patients suffering from sinonasal mucormycosis needs to be optimized with the help of early diagnosis [6]. An expeditious diagnosis needs awareness of warning signs among patients, high index of clinical suspicion, confirmation by appropriate modality and initiation of aggressive medical and surgical treatment [6]. SNM is primarily seen with patients who are immunocompromised, because of decrease phagocytic activity [2, 7]. The predisposing conditions which make covid-19 patients vulnerable to this disease are listed in Table 2 [6, 8]. The patients with SNM commonly present with myriad of symptoms and signs, which can be catalogued as nasal & paranasal sinus related, oral cavity related, orbit & periorbital related, facial symptoms and cerebral symptoms [9]. (Figure 1)

Presently, as the world is on the verge of culmination of the second wave of Covid-19, we try to single out factors responsible for the

sudden increment in the incidence of sinonasal mucormycosis [9, 10, and 11] among covid-19 patients along with symptoms & signs they presented with and discuss their imaging features on cross sectional modality.

## 2. Material and Methods:

The case records of 30 patients, between January to May, 2021, with positive RT-PCR (Reverse transcriptase-polymerase chain reaction) for COVID-19 and biopsy proven SNM were retrospectively evaluated for relevant clinical data. All 30 patients underwent MRI of orbit, paranasal sinuses and brain with contrast. The Magnetic Resonance Imaging (MRI) images were retrieved from the Picture Archiving and Communication System (PACS). MR imaging with following protocol were acquired (Table 3). MRI imaging was performed using 1.5 T Siemens (Avanto). Informed consent from all patients including the agreement for the data publication was taken.

## 3. Results:

### 3.1. Demographic and clinical data

We analysed the data of 30 patients who fulfilled our inclusion criteria, out of which 26 were male and 4 females. The age group of our sample size ranged from minimum of 28 years to 76 years, with mean age of 51.

The history of diabetes mellitus was taken from all patients on admission, among which 16 patients gave positive history. On comparing this, with the levels of HbA1c of all patients, 22 patients had raised HbA1c (above 6.4%), among which 7 patients died (31.8%); 5 were in pre-diabetic range (5.5% to 6.4%) and 3 patients had normal HbA1c. The mean HbA1c was 8.4% for patients who died, and 7.2% for those who are alive. The random blood glucose level of every patient was measured, 28 patients had raised random blood glucose at the time of admission, among which 7 patients died. The mean random blood glucose of patients who died was 283 mg/mol, and 261 mg/mol, in those who were alive.

Ferritin values was also measured for all patients, and it was observed that mean



ferritin level among patients who died was 842 ng/ml, which was significant by unpaired 'T' test with p-value < .001. High values of ferritin were confirmed in 24 patients (80%) among which 8 patients died.

18 (60%) patients needed service of intensive care units during their course of management, among which 7 (23%) patients died. The most common symptoms and number of patients who died and had these symptoms are shown in figure 2. We also tried correlating some common predisposing conditions concerned with the management of these patients. Among the 30 patients under consideration, 19 (63%) had received steroids and 16 (53%) patients were given supplemental oxygen. 8 (27%) patients underwent Functional Endoscopic Sinus Surgery (FESS) with surgical debridement, out of which 1 died, and for 3 (10%) patients exenteration were done, all of whom survived.

**3.2. Image analysis- Retrospective review by consensus was performed by 5 experienced radiologists, who were blinded to clinical and pathological data, to look for sites and extent of involvement and signal characteristics. As these patients presented at different stages of the disease, they were divided into four groups based on the extent of involvement and prognosis (Table 4).**

On imaging, scans of these patients were assessed for involvement of superficial cellulitis, orbit, neck spaces, paranasal sinuses and intracranial spread. Also, the signal intensity and contrast enhancement pattern were observed and assessed.

Superficial cellulitis in preseptal with prenasal extension and preantral involvement were assessed best on T2W axial and STIR coronal images (Table 5) (figure 3). 25 (83%) patients presented with superficial cellulitis, 22 of them had preseptal cellulitis, out of which 7 patients had right side involvement, 13 had left side involvement and 1 on both sides. 24 patients had preantral cellulitis, 10 on right, 12 on left and 1 patient showed bilateral involvement.

Nasal cavity involvement was determined by the appearance of T2 hypointense signal which showed heterogenous or no

enhancement of turbinate (which has been referred as "black turbinate sign" [12]) (Figure 4) on contrast T1W FS sequences (Table 6).

The complicity of palate and alveolar process was ascertained by the presence of STIR hyperintensity and by enhancement on contrast T1W FS sequences.

The appearance of paranasal sinuses (PNS) was isointense on T1W, heterogeneously hypointense in T2W. Two distinct enhancement patterns were observed – heterogenous enhancement and no enhancement with thick peripheral enhancing rim (Table 6).

Nasal cavity was involved in 18 patients, whereas 7 patients showed extension of the disease process to palate and adjacent alveolar process leading to palatal osteonecrosis seen as black patch over hard palate and loosening of teeth (Figure 5). Paranasal sinuses were involved in 28 patients, out of which the most commonly involved (in decreasing order) were bilateral ethmoid sinuses, left maxillary sinus followed by left ethmoid air cells and frontal sinus (Table 7).

Orbit involvement were seen in following pattern (Table 8 and 9), with most common pattern being extraconal compartment involvement. The most common intraconal muscle involved was medial rectus (left more common than right). The orbital compartment involvement was assessed on STIR coronal sequence. The intraconal involvement was ascertained as presence of fat stranding on STIR sequences. The ophthalmitis was best seen as abnormal enhancement on contrast T1W FS sequences. Optic nerve involvement was seen as STIR hyperintensity. The intraorbital muscle involvement along with muscle bulk were seen on T2W axial and coronal as well as STIR coronal sequences. (Figure 6 and 7) Orbital apex involvement was seen as fat stranding and altered signal on STIR and T2W sequences (Table 5) (Figure 9).

Neck space involvement were seen in following subcategories: Pterygoid muscle involvement (PM), Temporalis muscle involvement (TM), pterygopalatine fossa (PPF) and its communication with nasal cavity, sphenopalatine foramen (SPF), retro-maxillary



fat pad (RM) and pharyngeal mucosal space (PMS). The most common involvement was seen of PPF & SPF followed by pterygoid muscle involvement. (Table 10). These were seen as hyperintensity on STIR axial sequences and on contrast enhanced T1W FS sequences (Table 5) (Figure 8).

Intracranial extension was considered to be present if the patient presented with any of the following involvement: cavernous sinus (CS), cavernous segment of internal carotid artery (ICA), thickening and abnormal enhancement of dura matter along temporal convexities (DM), Meckel's cave (MC) and parenchymal involvement (PC). Intracranial extension according to above region involvement were seen in 16 patients (53%). The most frequent pattern of involvement (in decreasing order) was DM, CS, DM + CS, and MC. (Table 11) (Figure 9, 10, 11 and 12)

High Resolution CT thorax were performed for every patient and CT severity score were assigned for every patient [13]. The cut-off for mild cases were taken at score of 8. 23 (77%) patients had CT severity score of more than 8, out of which 6 patients (26%) died.

The mortality rate in our sample size was 26.7% (8 out of 30 patients) all of which were male.

The distribution of patients in various stages are shown in Table 12. Mortality was seen in 3 patients each of stage 3 and 4a, while 2 patients in stage 4b died.

#### 4. Discussion:

Mucormycosis is an invasive fungal infection. Different forms have been noted depending on the affected body part – sinonasal, pulmonary, gastrointestinal, cutaneous and disseminated mucormycosis, most common among which is sinonasal form.

The fungal spores are ubiquitous, and are believed to first germinate and infect nasal cavity and paranasal sinuses in patients with immunocompromised states [14]. The further dissemination of disease can occur to orbit, neck spaces and palate. Intracranial extensions in form of dural thickening, cavernous sinus and brain parenchymal involvement can also be seen. Imaging helps in determining the extent of disease and in surgical planning [15]. In early stages of

disease, it only presents as mucosal thickening in paranasal sinuses, and in such cases, it is necessary to have high clinical suspicion for diagnosis [14].

Mnif et al. and Herrera et al. have reported that the disease involves orbit and the changes can be interpreted on cross section imaging [16, 17]. Mohindra et al. has shown that cavernous sinus invasion and vascular involvement like internal carotid artery thrombus can be detected with MRI [18]. In our study cavernous sinus was involved in 17 cases and 4 patients showed thrombus in internal carotid artery. The affected area appears hypointense on T1W and T2W with homogenous enhancement on post contrast images [19].

The extrasinus involvement was seen with intact bones in many cases, likely suggesting perineural/perivascular spread of disease. The angioinvasive nature of disease were seen as presence of fat stranding in retro antral, premaxillary and preseptal regions [20]. However, few patients did present with bony erosions.

The nasal and paranasal sinuses showed presence of T2W hypointense signal in most patients, which may be due to presence of iron and manganese in fungal elements [21]. Post contrast images showed two types of patterns in paranasal sinuses, namely, heterogenous enhancement (14 patients) and thick peripheral rim enhancement with non-enhancing centre (12 patients). MRI is also useful in detecting palate and alveolar involvement (7 patients) which again shows the angioinvasive nature of disease [22].

Pathogenesis of sinonasal mucormycosis and its aggressive angioinvasive character in COVID-19 patients, especially diabetics can be attributed to [23, 24, and 25]:

- reduced phagocytic activity
- Increased accessibility of iron due to dissociation of iron-protein complexes by fungal heme oxygenase and transferrin acidic ph.
- Lymphopenia and decrease in CD4+ and CD8+ T cells which produce cytokines like interleukin (IL) 4, IL-10, IL-17 and interferon-gamma that are responsible for damage of fungal hyphae.



- Elevated glucose levels decrease antiviral response of body.
- In diabetics there is reduced activity of natural killer cell activity, skewed activity of T-cells and hyperactivity of pro-inflammatory M1 macrophages which play an important role in aggravating the severity.

Survival in these patients depends on early diagnosis and prompt medical and surgical treatment. The predisposing conditions such as uncontrolled diabetics must also be taken care of. The drug of choice is systemic amphotericin B, although its liposomal formulations are preferred due to its relatively lower nephrotoxicity. Surgical management depends on the extension of disease, with Functional endoscopic sinus surgery (FESS) and orbital exenteration being the most important surgical procedures along with surgical debridement. Posaconazole is an oral antifungal agent that has been used as step-down therapy after initial control of the mucormycosis. Unfortunately, we lost 8 patients in the span of five months despite of receiving systemic amphotericin B and surgical debridement.

Limitations of this study included absence of CT studies for all patients as this was not a part of protocol in our institution. Due to retrospective nature of the study, there were minor variations in MRI protocols. Also, due to retrospective nature of the study we were not able to take ADC values of all patients at areas of diffusion restriction.

### 5. Conclusion:

Based on our study, MRI played an important role in diagnosis and staging of sinonasal mucormycosis as well as determining the extrasinus extent of disease based on their appearances and enhancement patterns. Clinically most patients presented with raised Hb1Ac levels, random blood glucose and ferritin levels. Most patients presented with the CT severity score of more than 8 on HRCT Thorax. In our study more than half the patients required services of intensive care unit, received oxygen and steroids. Mortality was seen in patients who presented in advanced stage of the disease, with orbital or intracranial extension (Stage 3 and 4). Thus, it is imperative that high index of suspicion,

early imaging with diagnosis and aggressive management protocol (including medical anti-fungal medications and surgical debridement) needed to reduce morbidity and mortality. MR imaging plays very pivotal role in early diagnosis and staging of the disease and thereby help clinicians to do optimum management regime.

Acknowledgement – Statistician  
Dr.S.V.Kakade.

Conflict of Interest – None.

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Sep

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**Appendix A: Concise Master chart for all patients.**

Patient Number	Age	Sex	Received steroid during COVID treatment*	Supplemental Oxygen*	HbA1c	Random Glucose	Nasal cavity involved**	Paranasal sinus involvement**	Involvement of Orbit**	Extension to neck spaces and palate**	Intracranial extension**	HRCT thorax severity score	Stage of SNM	Outcome***
1	50	M	0	1	7.1	190	1	1	1	1	0	10	3	0
2	61	M	0	0	8.6	240	0	1	1	1	1	3	4b	0
3	28	F	1	1	6.4	170	0	1	1	1	1	12	4b	1
4	76	M	1	1	9.4	400	1	1	1	1	1	11	4a	0
5	66	F	1	1	9.5	310	1	1	1	1	1	0	4b	1
6	47	M	0	0	5.5	250	1	1	0	1	1	15	4a	0
7	66	M	0	1	10	314	1	1	1	1	0	7	3	1
8	52	M	1	1	9	275	0	1	1	0	0	12	3	0
9	70	M	0	0	8.7	260	0	1	1	1	0	15	3	0
10	52	M	1	1	7	220	0	1	1	0	1	18	4a	1
11	72	F	0	0	6.7	190	0	1	0	1	0	4	3	0
12	54	M	0	0	6.4	200	1	1	1	1	1	2	4b	0
13	35	M	1	0	7	250	0	0	1	1	0	12	3	1
14	58	M	1	1	5.1	220	0	1	1	1	1	14	4b	0
15	35	M	1	1	8	260	1	1	1	1	1	15	4a	1
16	40	M	1	1	9	320	0	0	1	1	1	17	4a	1
17	62	M	0	1	10	420	0	1	1	0	0	10	3	1
18	52	M	1	1	5.2	200	0	1	1	1	1	15	4a	0
19	36	M	1	1	7.4	237	1	1	0	0	0	11	2	0
20	55	F	1	1	6.5	387	1	1	0	1	1	10	4a	0
21	48	M	1	1	6.8	220	1	1	0	1	0	10	3	0
22	31	M	1	1	9.9	465	1	1	1	1	1	20	4a	0
23	40	M	1	0	5.4	74	1	1	0	1	0	10	3	0
24	52	M	1	0	9.1	400	1	1	0	1	0	16	3	0
25	52	M	1	0	7.4	350	1	1	1	1	1	12	4a	0
26	48	M	0	0	5.8	307	1	1	1	1	0	6	3	0
27	47	M	1	0	7.5	250	1	1	1	1	0	14	3	0
28	67	M	1	0	6.9	200	1	1	1	1	1	13	4a	0
29	41	M	0	0	7.4	240	0	1	1	1	0	5	3	0
30	40	M	0	0	5.9	194	1	1	1	1	1	11	4a	0

\* 1 – positive history, 0 – negative response; \*\* 1 – involved, 0 – not involved; \*\*\* 1 – Died, 0 – Alive

**TABELS**

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Kingdom	Fungi
Phylum	Zygomycota
Class	Zygomycetes
Subclass	Incertaedis
Order	Mucorales
Family	Mucoraceae
Genus	Mucor, Rhizopus and Absidia

Diabetes mellitus
Corticosteroid
Supplemental oxygen or mechanical ventilation
Haematological / solid organ malignancy
Organ transplantation



Iron overload

Table 3: MRI Brain with head, neck, paranasal sinus and orbit sequences.

For Brain:			
Sequence	TE (in milliseconds)	TR (in milliseconds)	FOV (in cm)
T2 axial	100	4240	19.4 x 23.0
T1 axial	10	419	19.4 x 23.0
FLAIR*	92	8640	17.2 x 24.0
T2 coronal	100	4240	19.4 x 23.0
T1 sagittal	10	419	22.3 x 25.5
For head, neck, paranasal sinus and orbit:			
T2 coronal	100	6270	15.8 x 21.0
T1 coronal	100	612	15.0 x 20.0
T2 FS axial	85	3200	14.8 x 19.0
T1 FS coronal	11	504	14.8 x 19.0
STIR coronal**	44	5140	15.4 x 19.0
TE- Time to Echo; TR- Repetition Time; FOV- field of view; FLAIR- Fluid attenuated inversion recovery; STIR- Short Tau Inversion Recovery; * inversion time (TI) of 2456 millisecond was combined with FLAIR; ** inversion time (TI) of 160 millisecond was combined with STIR.			

Table 4: Staging of SNM on the basis of extent of involvement

Stage 1	Nasal cavity only involved
Stage 2	Paranasal sinuses involvement
Stage 3	Orbit and/or neck space and palate involved
Stage 4a	Intracranial extension – cavernous sinus and/or dural and/or Meckel’s cave involvement.
Stage 4b	Intracranial extension – vascular involvement with/without parenchymal complication.

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Table 5: MRI characteristics and best sequences to examine them

	Sequence
Superficial cellulitis	T2W axial, STIR coronal
Extraconal/ intraconal orbital compartment	STIR coronal
Orbital muscle	T2W coronal, STIR coronal
Optic Nerve	STIR coronal
Ophthalmitis	Contrast T1W FS axial
Orbital apex	T2W coronal
Neck spaces	STIR axial, Contrast T1W FS axial
Nasal Cavity, paranasal sinuses	T2W coronal, Contrast T1W FS coronal
Palate, alveolar process	STIR coronal, Contrast T1W FS coronal
Cavernous sinus, Internal carotid artery	T2W coronal, Contrast T1W FS coronal
Dura matter	Contrast T1W FS axial
Parenchymal	T2W axial, Contrast T1W FS axial

Table 6: Enhancement pattern of paranasal sinuses and nasal turbinate

Enhancement Characteristic	Number of patients
Heterogenous enhancement in PNS	14
Thick peripheral rim enhancement with non-enhancing centre in PNS	12



Black turbinate sign	8
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	Maxillary	Sphenoid	Ethmoid	Frontal
Right	7	3	4	2
Left	11	3	9	9
Bilateral	8	7	12	1
Not Involved	4	17	5	18

Compartment involved	Number of Cases
Extraconal	20
Conal and Intraconal	19
Optic nerve	10
Ophthalmitis	06
Orbital apex	16

	Right	Left	Bilateral
Medial rectus	7	9	2
Superior oblique	7	7	2
Superior rectus	5	4	0
Inferior rectus and Inferior oblique	5	4	1
Lateral rectus	2	1	0

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Neck region involved	Number of patients
PM	16
TM	07
SPF & PPF	25
RM	23
PMS	10

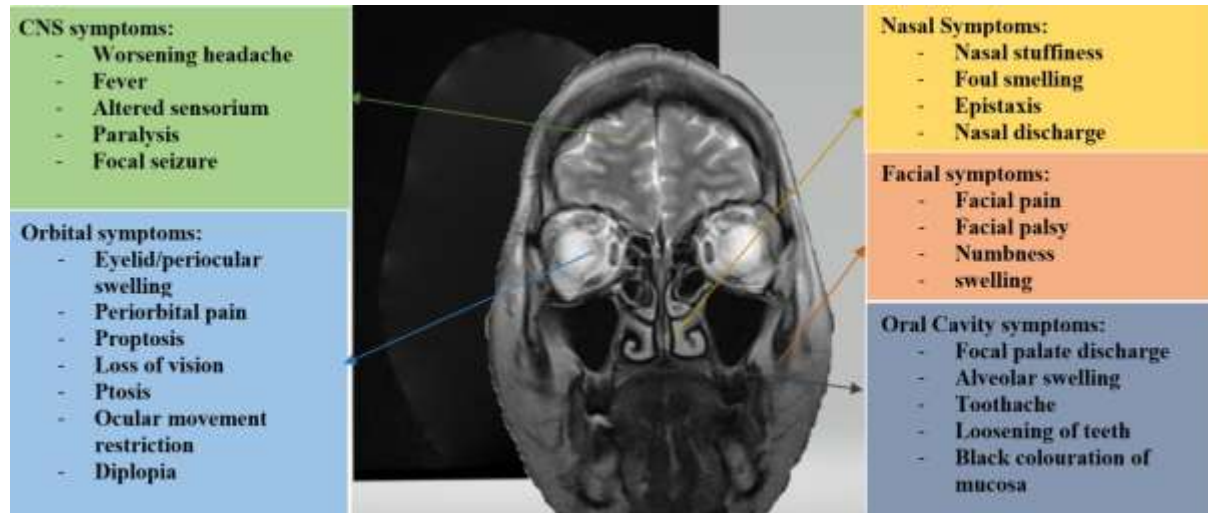
	Number of patients	% (out of patients showing intracranial involvement)
DM	11	68.7
CS	10	62.5
CS + DM	7	43.7
MC	6	37.5
ICA	4	25.0
PC	3	18.6

	Number of patients	mortality
Stage 1	0	0
Stage 2	1	0
Stage 3	13	3



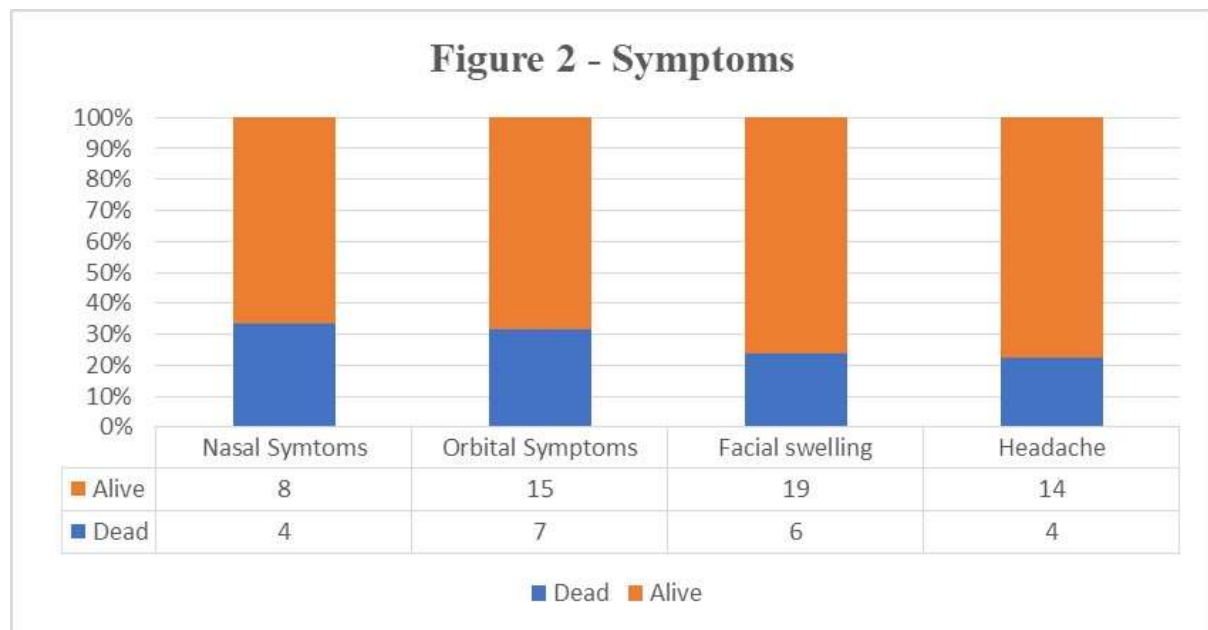
Stage 4a	11	3
Stage 4b	5	2

**IMAGES**



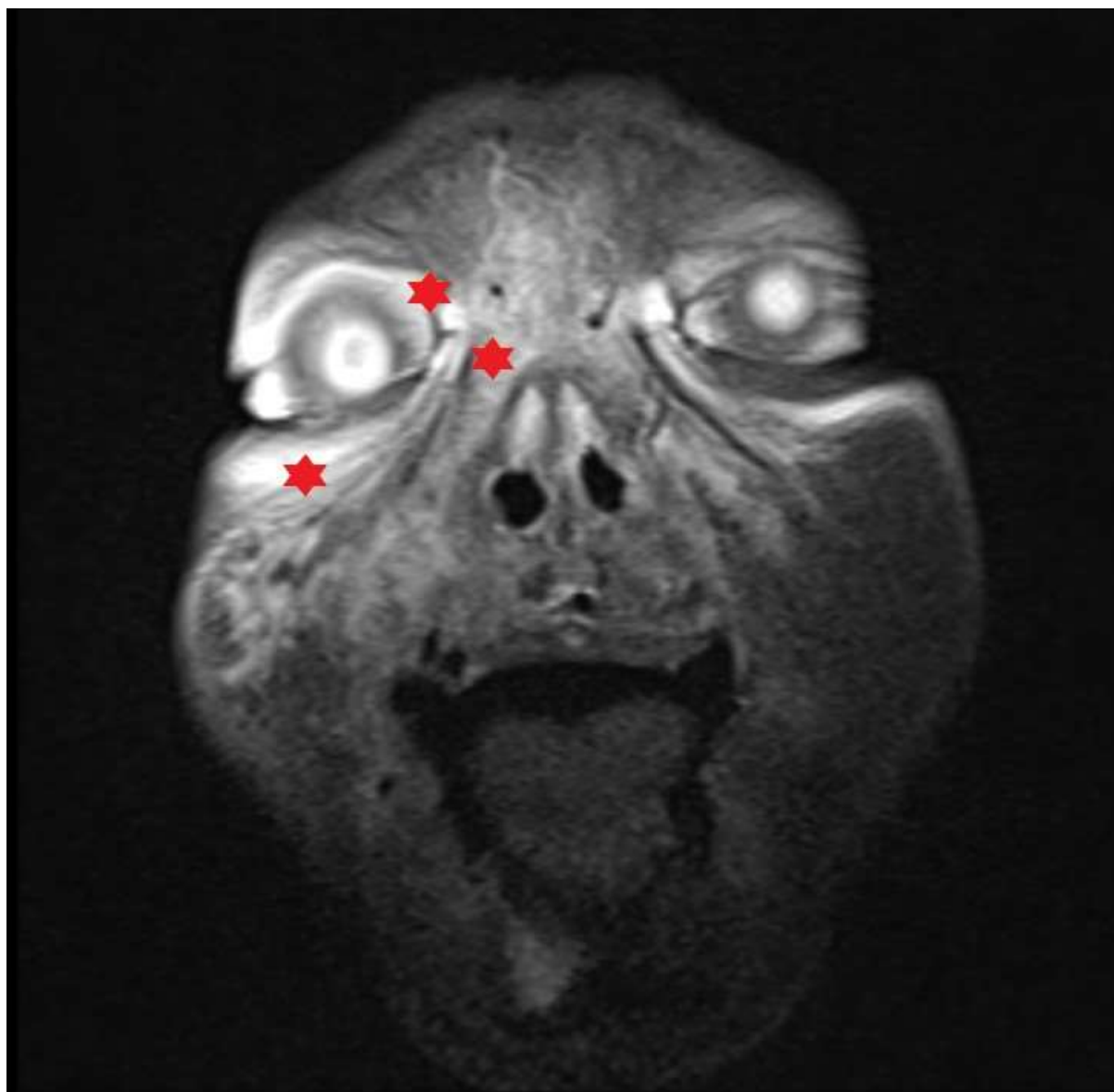
**IMAGE 1**

7374



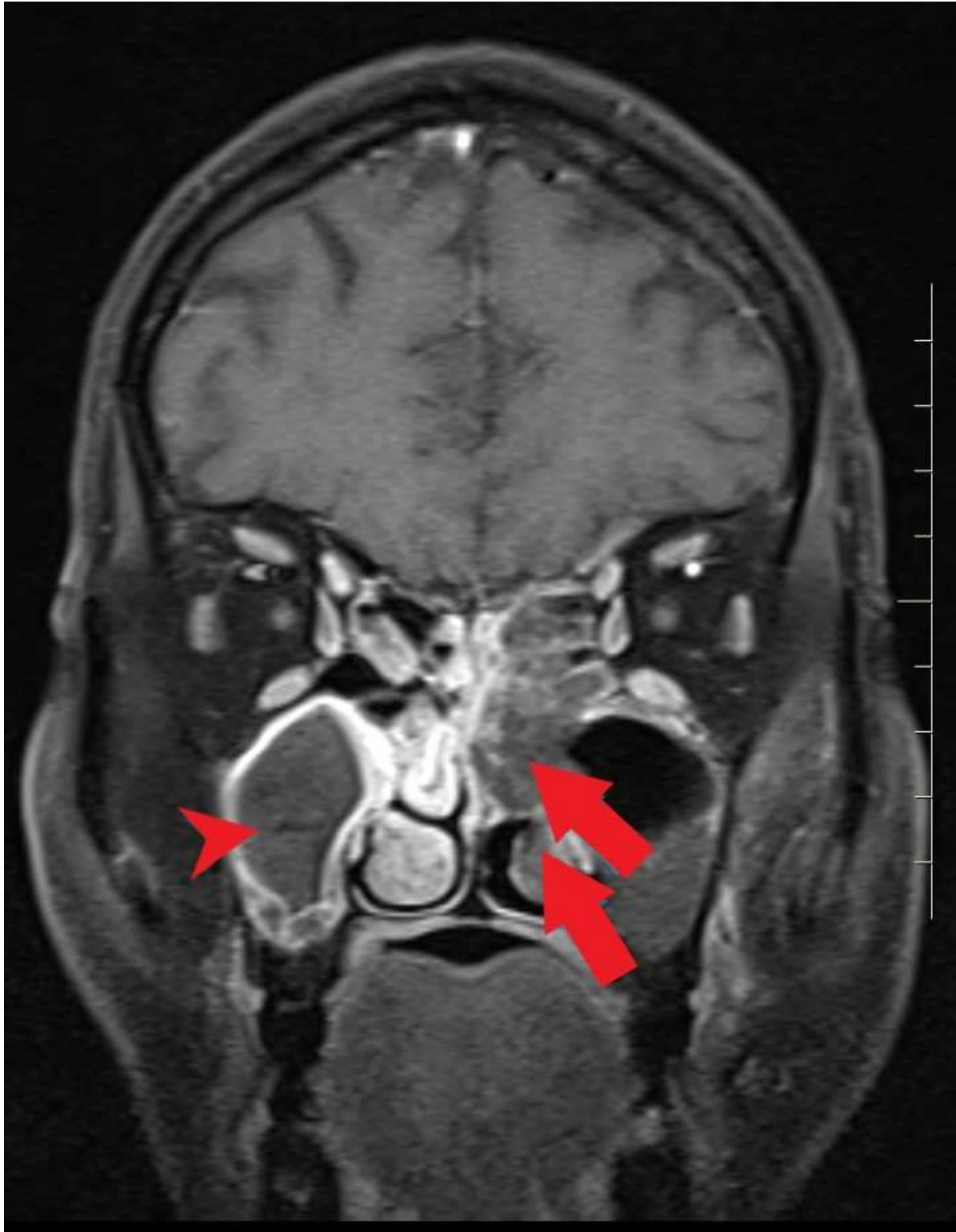
**IMAGE 2**





7375

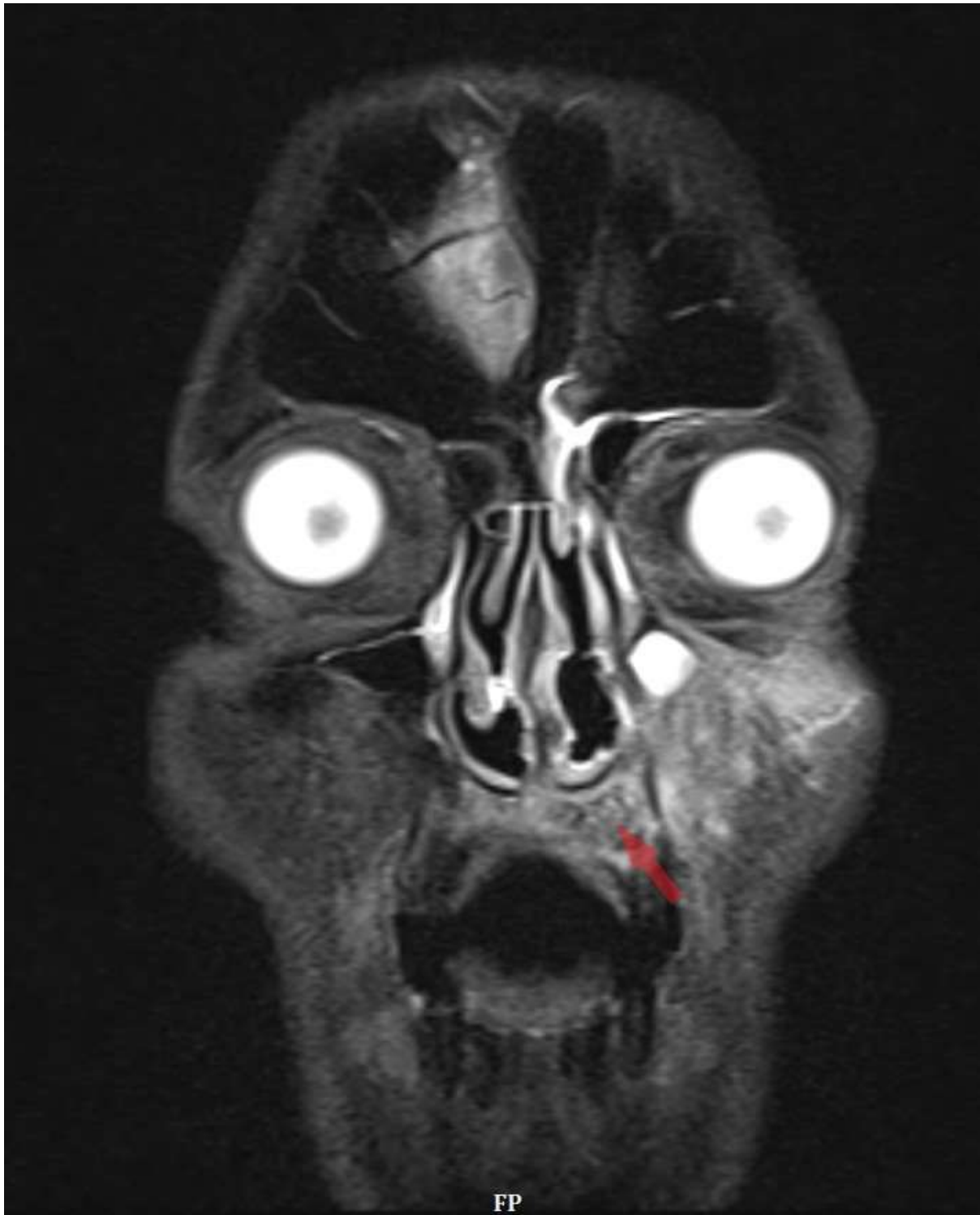
**IMAGE 3**



7376

IMAGE 4





7377

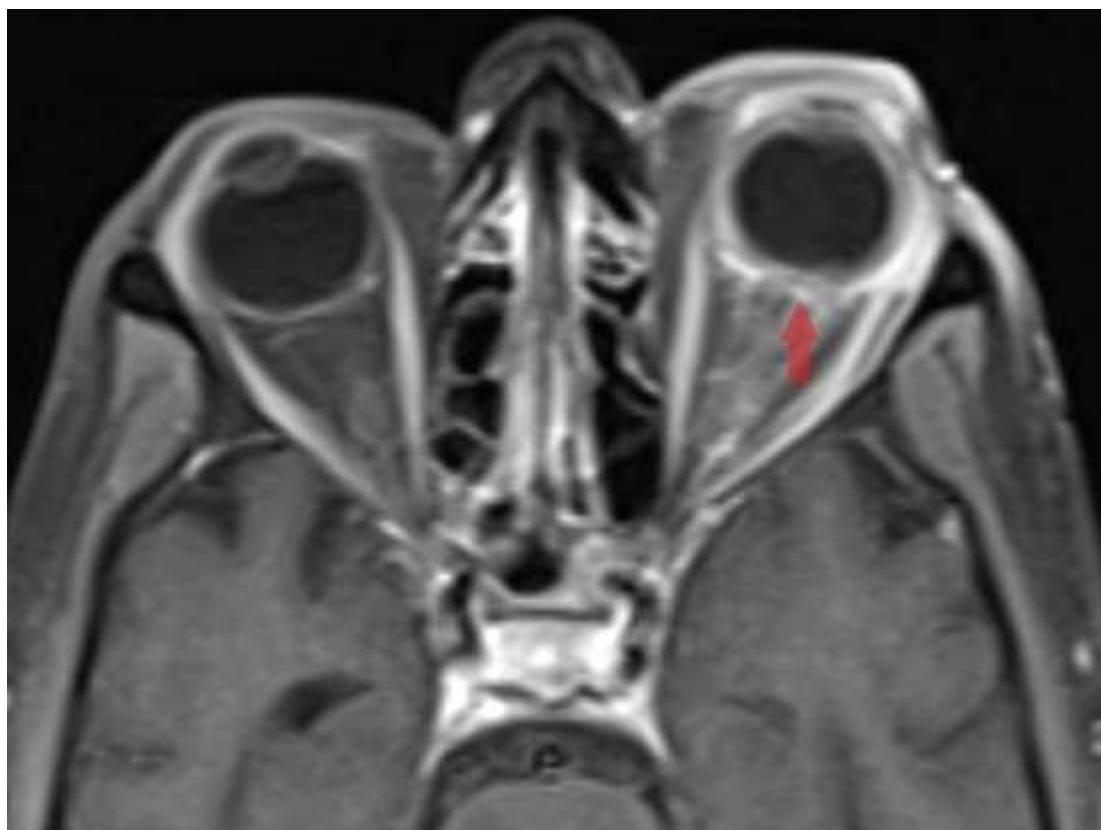
IMAGE 5



7378

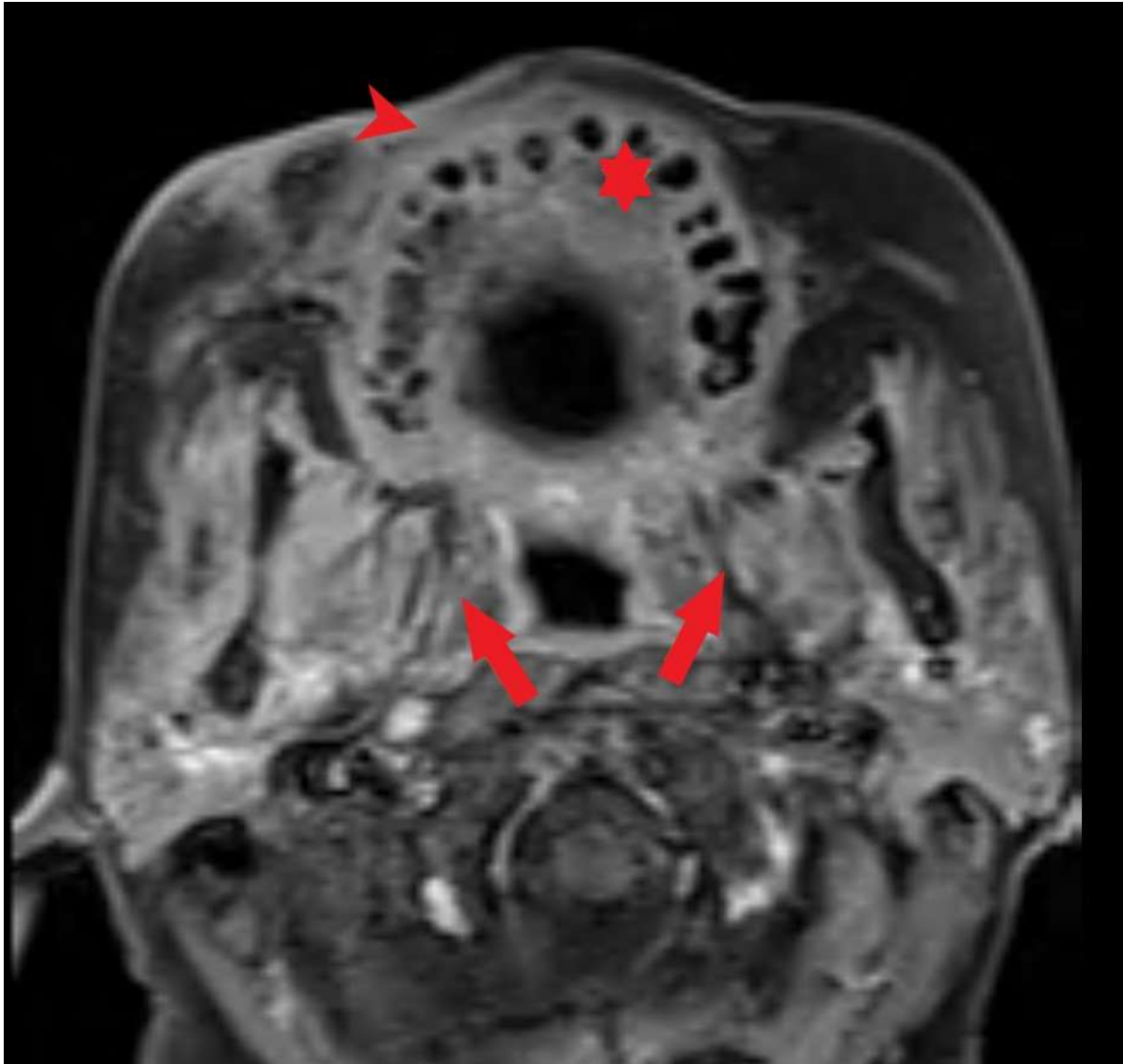
IMAGE 6





7379

**IMAGE 7**



**IMAGE 8**



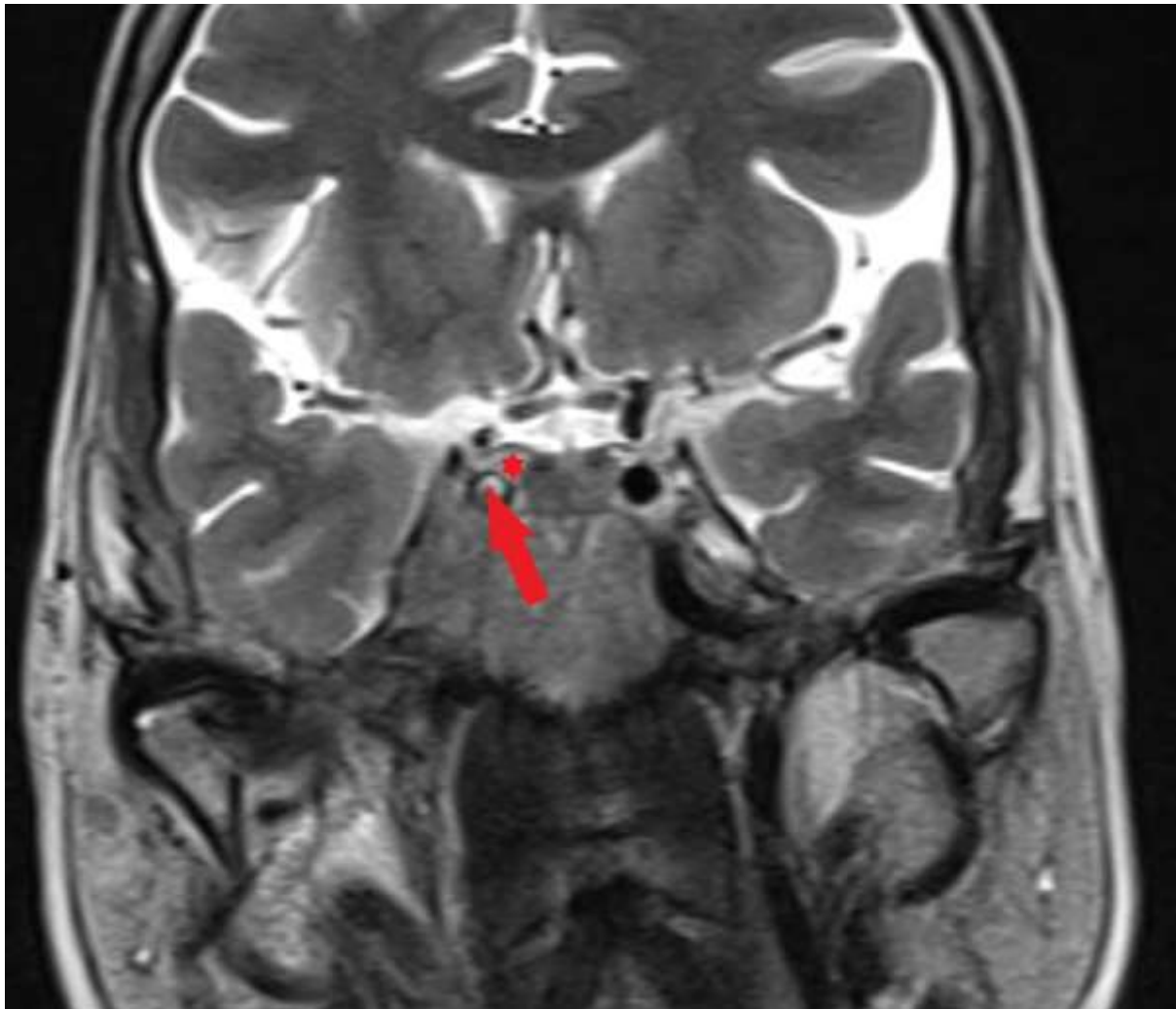
7381

**IMAGE 9**



7382

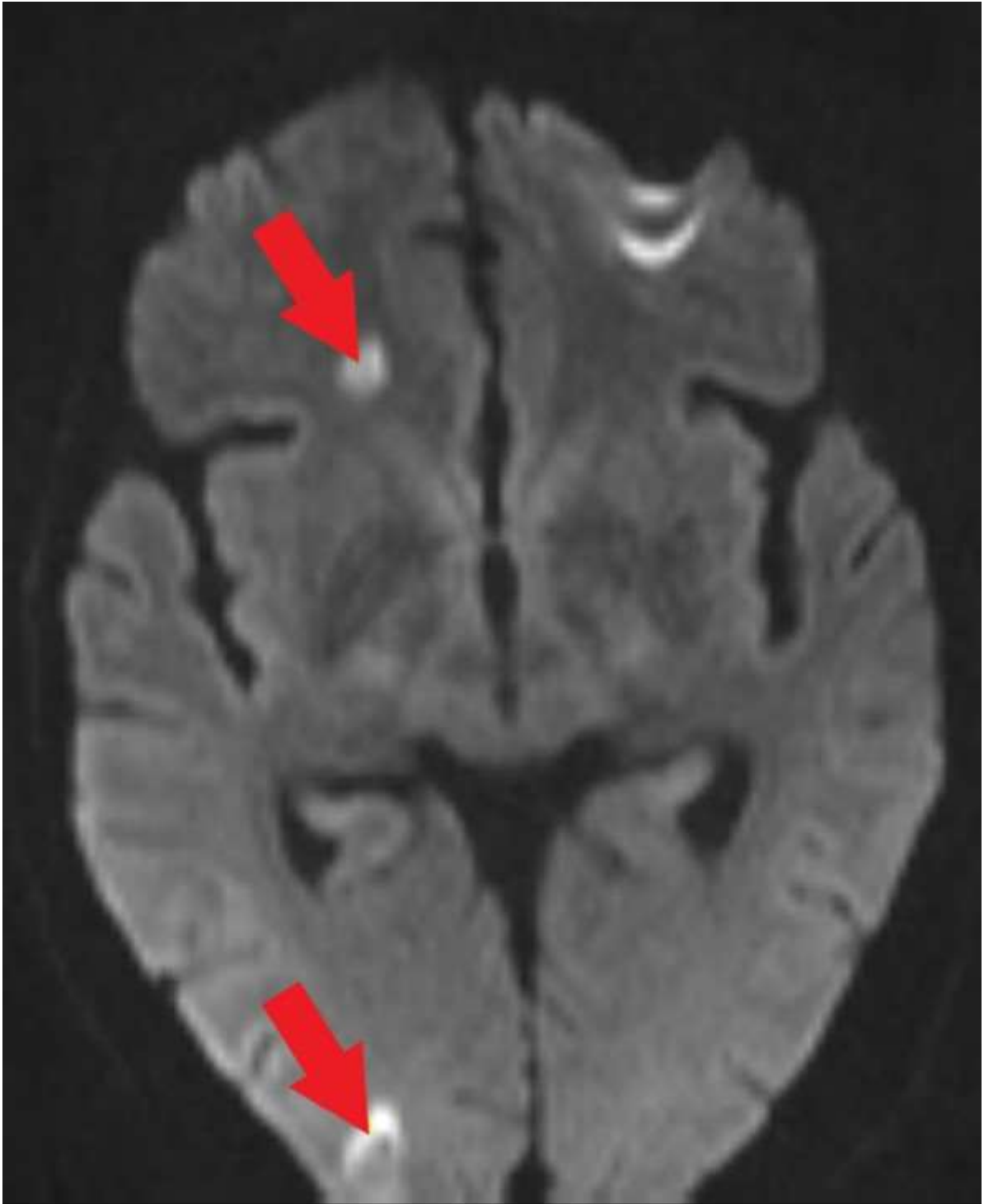
**IMAGE 10**



7383

IMAGE 11





7384

**IMAGE 12**

**Figure Captions:**

Figure 1 Signs and symptoms in patients of SNM.

Figure 2 – Distribution of symptoms in patients of SNM.



Figure 3 - In a case of sinonasalmucormycosis, STIR coronal section shows heterogenous hyperintensity along preantral, prenasal and preseptal regions on right side indicating superficial cellulitis (asterisk).

Figure 4 - Black turbinate – T1W FS post contrast coronal section shows no enhancement of inferior and middle turbinate on left side, referred as “black turbinate sign” (arrows). Right maxillary sinus shows non enhancing collection with thick peripheral enhancement (arrowhead). Features suggestive of sinonasalmucormycosis.

Figure 5 - In a biopsy proven case of sinonasalmucormycosis, STIR coronal section show heterogenous hyperintensity in anterior aspect of left half of hard palate indicating its involvement (arrow). There is also presence of preantral cellulitis on left side.

Figure 6 - Orbital involvement in sinonasalmucormycosis - STIR coronal section shows hyperintensity in optic nerve (arrow). There is heterogenous hyperintensity with fat stranding noted in Intraconal region with involvement of recti muscles.

Figure 7 - Orbital involvement in sinonasalmucormycosis - T1W FS post contrast axial section show thickening and irregularity at the posterior surface of eyeball in sclera region (arrow). Intra conal area and preseptal region also shows heterogenous irregularity.

Figure 8 - T1W FS post contrast axial section shows extension of sinonasalmucormycosis to neck spaces (masticator space - arrow) and hard palate (asterisk) with oedema and thickening of adjacent subcutaneous tissue (arrowhead).

7385

Figure 9 - In a biopsy proven case of sinonasalmucormycosis, T1W FS post contrast axial section shows dural thickening along right temporal convexity which exhibits abnormal enhancement (arrow). Abnormal enhancing soft tissue are also seen involving bilateral orbital apex and cavernous sinus with extension and thrombus in cavernous segment of right internal carotid artery.

Figure 10 - On T2W axial section heterogenous hypointense signal is noted in Meckel’s cave on both sides (arrow). Similar signal intensity is also noted in bilateral sphenoid and ethmoid sinuses indicating involvement by the disease process.

Figure 11 - Cavernous sinus invasion and vascular thrombus in a case of sinonasalmucormycosis - T2W coronal section shows loss of flow void in cavernous segment of internal carotid artery on right side (arrow). Heterogenous hypointense signal is seen in right cavernous sinus (asterisk).

Figure 12 - In a case of sinonasalmucormycosis with vascular thrombus in in cavernous segment of internal carotid artery on right side, foci of DWI (b value- 1000) hyperintensity in right middle cerebral artery territory (arrow) which showed corresponding decrease ADC values (not shown in figure), suggestive of lacunar infarct.

