

Rhino Orbital Cerebral Mucormycosis in settings of Covid-19 infection: A Case Series of Thirteen Patients

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Abstract

Background

Rhino-Orbital-Cerebral Mucormycosis (ROCM) is an important infectious disease encountered in huge number in this recent post-covid 19 era. An alteration in defence immune system during covid-19 illness, in the presence of uncontrolled hyperglycaemia has led to the new epidemic of ROCM especially in developing nations like India.

Method

This case series of thirteen patients illustrates the various clinical presentation, laboratorial parameters, imaging features and outcome of patients of ROCM admitted in a tertiary care hospital in Northern India.

Result

In our case series, a total of 13 newly diagnosed cases of Rhino-Orbital-Cerebral Mucormycosis were studied. History of covid-19 illness was observed in 7 cases (53.8%), use of steroid during Covid-19 illness was seen in 5 cases (38.5%), oxygen therapy was given in 4 cases (30.8%). Co-morbid state in the form of diabetes mellitus was present in 12 cases (92.3%) with mean duration 16.69 months with an important finding of 6 cases (46.2%) having new-onset diabetes; hypertension in present in 3 cases (23.1%). Magnetic resonance imaging of paranasal sinuses showed involvement of multiple sinuses in all the 13 cases(100%), including maxillary and ethmoidal sinuses, with frontal in 12 cases (92.3%), sphenoidal in 11 cases (84.6%), symmetric in 9 cases (69.2%), mastoiditis in 4 cases (30.8%), maxillary space involvement in 4 cases (30.8%), palatal involvement in 1 case (7.7%). Multi-speciality approach treatment was given in the liposomal amphotericin B therapy in all the patients along with thorough endo-nasal debridement done in all cases, transcutaneous retrobulbar amphotericin B in 6 cases (46.2%) with exenteration done in 7 patients (53.9%). At 3 months of follow-up, there was substantial clinical improvement in all the cases.

Conclusion

There should be definite emphasis on high suspicion of mucor clinically for early diagnosis and aggressive management at initial state of diagnosis for better outcome. The need for sustained proper glycemic control during covid 19 era along with judicious use of steroid and public awareness for early symptoms and manifestations of mucor can curb the magnitude of such potentially opportunistic epidemic to a substantial rate. The longer the infection remains undetected, the greater the devastation ROCM can impose, of which blindness is an important hazard.

Introduction

Rhino-Orbital-Cerebral Mucormycosis is an important infectious disease encountered in huge number in this recent post-covid 19 era. Mucor has been present for long time in medical history, but several epidemics has highlighted its morbid outcome^[1]. An alteration in immune defence system during covid-19 illness, in the presence of uncontrolled hyperglycaemia has led to the new epidemic of ROCM especially in developing nations like India. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators^[2]. Phycomycosis/zygomycosis was first described in 1885 by Paltauf and later coined as 'Mucormycosis' in 1957 by Baker an American pathologist for an aggressive infection caused by *Rhizopus*^[2, 3, 4]. The *Rhizopus Oryzae* is most common type and responsible for 90% of Rhino-orbital-cerebral form^[5]. The mode of contamination is through the inhalation of fungal spores. India, being the Diabetes capital of world along with second most country affected by covid-19 illness lead to epidemic of ROCM recently^[6, 7, 8, 9]. There have been multiple but sparse case series globally depicting the clinical profile, laboratorial workup, imaging

features in ROCM in the past, but during post-covid 19 state esp the second wave, there is a vast increase in ROCM cases throughout Indian population [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21].

The diagnosis of ROCM is confirmed after detection of fungal spore along with correlation of imaging in the background of clinical profile. The 1950 Smith and Krichner criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include: [2, 22]

- (i) Black, necrotic turbinate's easily mistaken for dried, crusted blood,
- (ii) Blood-tinged nasal discharge and facial pain, both on the same side,
- (iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration,
- (iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and,
- (v) Multiple cranial nerve palsies unrelated to documented lesions.

The treatment of such aggressive disease is multidisciplinary efforts. Antifungal like intravenous amphotericin B or isavuconazole, followed by oral posaconazole are the main medical therapy, with good debridement of local nasal tissue debris, transcutaneous retrobulbar amphotericin B injections, timely exenteration being the corner-stone of treatment [23,24,25,26,27,28,29]. Sustained euglycaemia yields better results in outcome [30, 31, 32, 33, 33, 34, 35, 36, 37]

Objective

This case series of 13 patients illustrates the various clinical presentation, laboratorial parameters, imaging features and outcome of patients of ROCM admitted in a tertiary care hospital in Northern India.

Method

We studied the demographics, clinical presentation, laboratorial profile, imaging features and clinical outcome in 13 patients of newly diagnosed cases of Rhino-Orbital-Cerebral Mucormycosis. All the patients were thoroughly evaluated, treated as per standard protocols and staging and followed-up at 3 months from being discharged. The consent were obtained from all patients or their relatives/local guardians.

Result

In our case series, a total of 13 newly diagnosed cases of Rhino-Orbital-Cerebral Mucormycosis were studied with the youngest being 17 years old and eldest being 75 years age with a mean age of 47.69 years. The male: female ratio observed was 0.625 (5:8). History of covid-19 illness was observed in 7 cases (53.8%), use of steroid during Covid-19 illness was seen in 5 cases (38.5%), oxygen therapy was given in 4 cases (30.8%). Co-morbid state in the form of diabetes mellitus was present in 12 cases (92.3%) with mean duration 16.69 months with an important finding of 6 cases (46.2%) having new-onset diabetes; hypertension in present in 3 cases (23.1%). The most common presentation was nasal discharge, headache and swelling of eye which was seen in all 13 patients (100%), followed by dimness of vision in 9 cases (69.2%), fever seen in 8 cases (61.5%), gradual onset loss of vision (blindness) in 7 cases (53.9%), toothache and facial numbness in 7 cases (53.9%), facial weakness in 6 cases (46.2%) with cough in 3 patients (20.1%). Of due note was the duration of illness and presentation to hospital set-up which was 31.54 days on an average. Among the important signs, sinusitis was observed in all 13 cases (100%) with involvement of maxillary and ethmoidal in all cases and symmetry observed in 9 cases (69.2%), complete ophthalmoplegia in 8 cases (61.5%), perception of light negative in 6 cases (46.2%), lower motor neuron facial palsy in in 6 cases (46.2%), fundus abnormality in 4 cases (30.8%), Relative afferent pupillary defect (RAPD) in 2 cases (15.4%), palatal defect with pus discharge in 1 case (7.7%). The laboratorial workup showed anemia in 8 cases (61.5%), raised C reactive protein in all 13 cases (100%) with a mean of 48.23 units, procalcitonin <0.05 in all cases, hyponatremia in 12 cases (92.3%), hypokalemia in 11 cases (84.6%), hypocalcemia in 13 cases (100%), hyperglycemia in 12 cases (53.8%), hyperferritinemia in 8 cases (61.5%), elevated lactate dehydrogenase in 4 cases (30.8%), transient renal injury in 1 case (7.7%), while tranaminitis or hyperbilirubinemia was not observed. Fungal detection in nasal scrapping via KOH mount was positive for all the cases (Figure-1). The imaging profile under ROCM protocol had clinical correlation and magnetic resonance imaging changes were observed in all cases (100%) in paranasal sinuses and orbit with involvement of brain was detected in imaging in 9

cases (69.2%). Magnetic resonance imaging of paranasal sinuses showed involvement of multiple sinuses in all the 13 cases(100%), including maxillary and ethmoidal sinuses, with frontal in 12 cases (92.3%), sphenoidal in 11 cases (84.6%), symmetric in 9 cases (69.2%), mastoiditis in 4 cases (30.8%), maxillary space involvement in 4 cases (30.8%), palatal involvement in 1 case (7.7%)(Figure-2). MRI imaging of orbit showed ocular involvement in all the 13 cases (100%) with bony involvement seen in all the 13 cases (100%), extra-ocular muscles involvement in 12 cases (92.3%), optic nerve involvement in 7 cases (53.9%), and orbital apex involvement in 6 cases (46.2%), with one case of symmetric involvement of both eyes (7.7%)(Figure-2). Mri of brain showed involvement in 9 cases (69.2%), mostly temporal dural enhancement seen in 8 cases (61.5%), erosion of cribriform plate in 5 cases (38.5%), cavernous sinus involvement in 4 cases (30.8%), loss of internal carotid artery flow void in 3 cases (23.1%), infarct in 1 case (7.7%) and cerebritis in 1 case (7.7%) without any case showing symmetry(Figure-3). Majority of cases were suffering from stage 4 of ROCM (total 9 cases) and rest 4 were having stage 3 ROCM. Multi-speciality approach treatment was given in the liposomal amphotericin B therapy in all the patients along with thorough endo-nasal debridement done in all cases(Figure-4), transcutaneous retrobulbar amphotericin B in 6 cases (46.2%) with exenteration done in 7 patients (53.9%). The mean duration of hospital stay was 36.69 days with no mortality. At 3 months of follow-up, there was substantial clinical improvement in all the cases in the clinical parameters of headache (2 cases), swelling of eye (3 cases), nasal discharge (one case), fever (none), residual facial weakness (3 cases), but numbness of face persisted in all the previous 7 cases to some extent, with no new symptoms during follow-up. Radiological de-staging of ROCM was observed in all the cases at follow-up.

Discussion

This case series showed a slightly earlier mean age of presentation of 47.69 years as compared to other studies showing above 55 years^[6,13,21,34,34,36,37]. The sex ratio is showing female dominance as compared to male dominance in other case series^[6, 13, 21]. The presence of diabetes mellitus is 92.3% which correlates with other case series globally. ²¹

The detection of new onset diabetes in our series is 46.2% which was higher than previously noted in reports. The phenomena of naïve hyperglycaemic status along with covid illness might trigger to hypothesis of immune dysregulation in early diabetes precipitating opportunistic infectious diseases like ROCM. Sinusitis along with ocular involvement in some form was evident in all the cases at presentation to admission. The mean duration of illness was 31.54 days with earliest of 15 days and maximum of 45 days was observed which is quite late than other studies^[13]. Blindness was seen in seven cases (53.9%), orbital apex syndrome seen in 6 cases (46.2%), complete ophthalmoplegia seen in 8 cases (61.5%): a higher involvement basically is being observed as compared with other studies^[6,13,21].

Multiple paranasal sinuses were involved and majority showed the involvement of maxillary and ethmoidal sinuses, this was also seen in some other studies. A greater number of cases showed nervous system involvement 69.2%, which is higher than other case series Hence most of the patients were seen in stage 4 with higher neurological manifestations ^[6, 13, 21, 28]. The reason probably was due to late presentation of patients, by the time the disease has already progressed. Debridement of endonasal necrotic tissues were successfully done with regular follow-up in all cases. The use of transcutaneous retrobulbar amphotericin B was done in 7 cases of appropriate staging helped regression of further intraocular damage. The rate of exenteration was 53.9% which was quite higher due to increased cases of blindness at presentation ^[13]. Aggressive surgico-medical management with strict glycaemic control lead to better outcome.

Conclusion

Rhino-orbital-cerebral mucormycosis is a potentially treatable aggressive fungal disease of sino-ocular-neural system. A high degree of suspicion for mucor in all the cases of rhino-sinusitis along with aggressive management at disease onset itself are the keys to early prevention of such destructible course in ROCM illness. Proper glycemic control is advocated amidst the covid-19 era along with judicious use of steroid whenever indicated as there are increased cases of ROCM with newly detected diabetes mellitus. Multi-disciplinary team approach will result in better outcome. There is need for further awareness among public as well as primary-care physicians regarding early possible symptoms of ROCM and necessity of early antifungal initiation to curb the magnitude of such potentially treatable opportunistic epidemic to a substantial rate. The longer the infection remains undetected, the greater the devastation ROCM can impose, of which blindness is an important hazard. The delay in diagnosis and proper treatment directly affects outcome in ROCM.

Declarations

Ethics: Patients were consented and institutional ethical committee approval obtained.

Competing Interests: The authors declare no competing interest.

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Tables

TABLE 1 : CLINICOLABORATORICAL PROFILE OF ROCM PATIENTS

	PT 1	2	3	4	5	6	7	8	9	10	11	12	13	TOTAL
AGE	63	75	35	56	46	58	50	45	42	17	45	40	48	47.69 Mean
SEX (M:F)	M	F	F	F	F	F	M	M	F	M	F	F	M	5:8 (0.625)
COVID + STATUS	-	+	+	+	-	+	-	-	+	+	+	-	-	7/13(53.8%)
STEROID USE	-	+	+	-	-	+	-	-	-	+	+	-	-	5/13(38.5%)
OXYGEN USE	-	+	+	-	-	+	-	-	-	-	+	-	-	4/13(30.8%)
DIABETES MELLITUS	+	+	+	+	+	+	+	+	+	-	+	+	+	12/13(92.3%)
DURATION OF DM (months)	12	1	1	1	1	48	2	6	24	-	48	72	1	16.69 month
HYPERTENSION	-	+	-	-	-	-	+	-	-	-	+	-	-	3/13(23.1%)
FEVER	-	+	+	+	+	+	+	-	-	+	+	-	-	8/13(61.5%)
COUGH	-	+	+	-	-	-	-	-	-	-	+	-	-	3/13(20.1%)
DURATION OF ILLNESS (days)	30	45	45	45	45	40	30	20	30	15	20	20	25	31.54 days
NASAL DISCHARGE	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
HEADACHE	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
EYE SWELLING	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
DIMNESSESS VISION	-	+	-	-	+	+	+	+	+	+	-	+	+	9/13(69.2%)
BLINDNESS	-	+	-	-	-	-	+	+	+	+	-	+	+	7/13(53.9%)
TEETH PAIN	+	-	-	-	+	+	+	-	-	-	+	+	+	7/13(53.9%)
FACIAL WEAKNESS	-	+	-	+	+	+	-	-	+	-	-	+	-	6/13(46.2%)
FACIAL NUMBNESS	-	+	-	+	+	+	+	-	-	-	+	-	+	7/13(53.8%)
RAPD	-	-	-	-	-	-	-	+	-	+	-	-	-	2/13(15.4%)
COMPLETE OPHTHALMOPLEGIA	-	+	-	-	+	+	+	+	+	+	-	+	-	8/13(61.5%)
FUNDUS ABNORMALITY	-	+	-	-	-	-	+	-	+	-	-	+	-	4/13(30.8%)
ANEMIA	+	+	+	+	-	+	+	-	+	-	-	+	-	8/13(61.5%)
CRP	66	51	106	102	65	74	23	17	57	20	51	18	42	48.23
HYPONATREMIA	+	+	+	+	+	+	+	+	-	+	+	+	+	12/13(92.3%)
HYPOKALEMIA	+	+	+	+	+	-	-	+	+	+	+	+	+	11/13(84.6%)
HYPOCALCEMIA	+	+	+	+	+	+	+	+	-	+	+	+	+	13/13(100%)
RENAL INJURY	-	+	-	-	-	-	-	-	-	-	-	-	-	1/13(7.7%)
TRANSAMININTIS	-	-	-	-	-	-	-	-	-	-	-	-	-	0
ELEVATED LDH	-	+	-	-	-	+	-	-	+	+	-	-	-	4/13(30.8%)
HYPERGLYCEMIA	+	+	+	+	+	+	+	+	+	-	+	+	+	12/13(92.3%)
HYPERFERRITINEMIA	+	+	+	+	-	+	-	+	-	-	-	+	+	8/13(61.5%)
MRI PNS CHANGES	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
MRI ORBIT CHANGES	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)

MRI BRAIN CHANGES	-	+	-	+	+	+	+	+	-	+	-	+	+	9/13(69.2%)
STAGE OF ROCM	3	4	3	4	4	4	4	4	3	4	3	4	4	4 IN 9/13
KOH +	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
SYSTEMIC AMPHOTERICIN	+	+	+	+	+	+	+	+	H	+	+	+	+	12/13(92.3%)
RETROBULBAR AMPHOTERICIN	+	-	+	+	+	+	-	-	-	-	+	-	-	6/13(46.2%)
EXENTERATION	-	+	-	-	-	-	+	+	+	+	-	+	+	7/13(53.9%)
ENT DEBRIDEMENT	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13(100%)
DURATION OF STAY (days)	28	32	33	30	40	40	23	33	43	40	43	52	40	36.69 days
FOLLOW-UP														

I-Improved

TABLE 2 : MRI PROFILE OF ROCM PATIENTS

	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8	PT9	PT10	PT11	PT12	PT13	TOTAL
MRI BRAIN:-	9/13													
DURAL ENHANCEMENT	-	B	-	-	L	L	R	R	-	R	-	L	L	8
CEREBRITIS	-	-	-	-	-	-	-	-	-	R	-	-	-	1
ABSCESS	-	-	-	-	-	-	-	-	-	-	-	-	-	0
CAVERNOUS SINUS INVOLVEMENT	-	R	-	L	-	L	R	-	-	-	-	-	-	4
ICA LOSS OF FLOW VOIDS	-	R	-	-	-	L	R	-	-	-	-	-	-	3
INFARCT	-	-	-	-	-	-	R	-	-	-	-	-	-	1
HEMORRHAGE	-	-	-	-	-	-	-	-	-	-	-	-	-	0
CRIBRIFORM PLATE EROSION	-	+	+	-	-	-	-	+	-	-	+	+	-	5
SYMMETRICITY	-	-	-	-	-	-	-	-	-	-	-	-	-	0
MRI ORBIT:-	13/13													
BONY EROSION	R	B	L	L	L	L	R	R	R	R	L	L	L	13
INVOLVEMENT OF EXTRA-OCULAR MUSCLES	R	B	L	-	L	L	R	R	R	R	L	L	L	12
OPTIC NERVE INVOLVEMENT	-	R	-	-	-	-	R	R	R	R	-	L	L	7
ORBITAL APEX SYNDROME	-	R	-	-	-	-	R	R	R	R	-	L	-	6
SYMMETRICITY	-	+	-	-	-	-	-	-	-	-	-	-	-	1
MRI PNS:-	13/13													
MAXILLARY SINUSITIS	B	B	B	B	L	B	B	B	R	R	L	L	L	13
ETHMOIDAL SINUSITIS	B	B	L	L	L	B	B	B	R	R	B	L	B	13
FRONTAL SINUSITIS	R	B	-	L	L	L	L	R	R	R	L	L	R	12
SPHENOIDAL SINUSITIS	R	B	-	L	L	B	B	B	R	R	L	L	-	11
MULTIPLE SINUSES	+	+	+	+	+	+	+	+	+	+	+	+	+	13
BILATERAL SINUSES	ME S	ME S F	M	M	-	ME S	ME S	ME S	-	-	E	-	E	9
MASTICATORY SPACES	+	-	-	-	+	+	+	-	-	-	-	+	+	6
MASTOIDITIS	-	B	-	-	-	L	-	-	-	-	R	L		4
PALATAL	-	-	-	-	-	-	-	-	-	-	-	-	L	1

B - bilateral, L - left, R - right

Sinuses : M - maxillary, E - Ethmoid, S- sphenoid, F- frontal

Figures

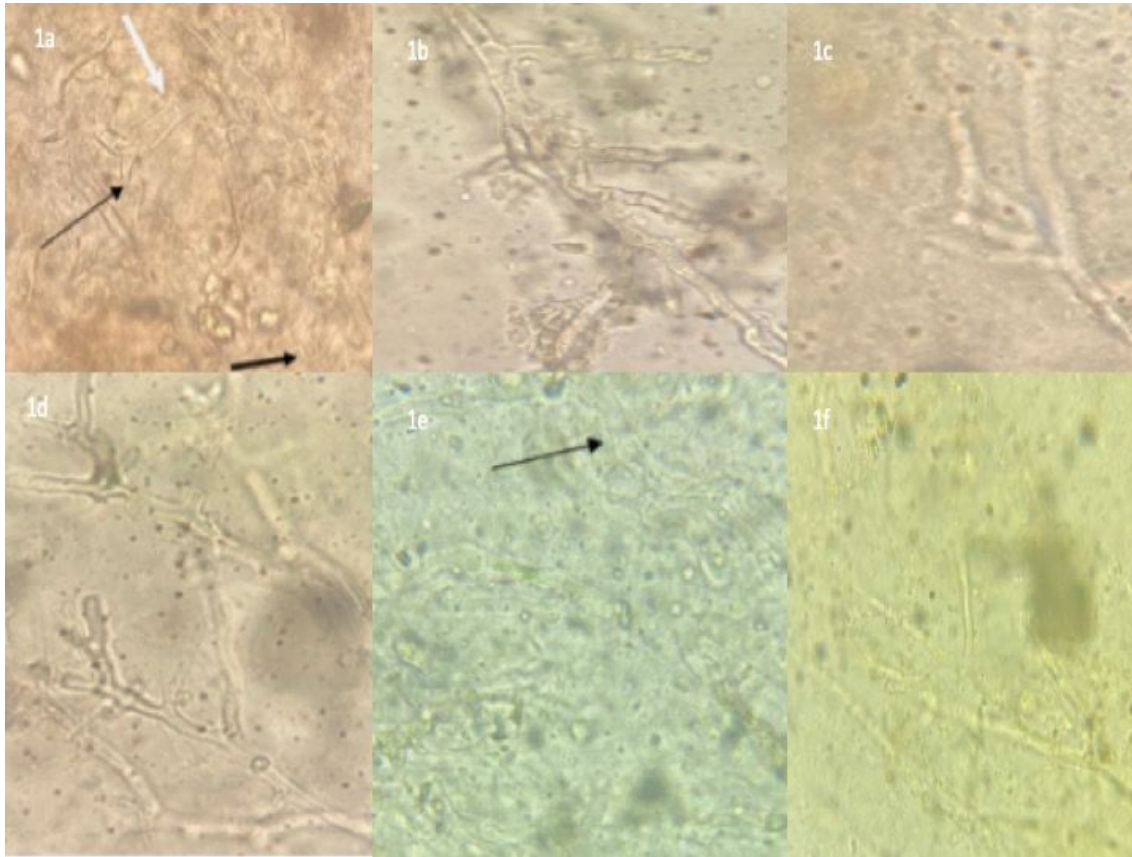


Figure 1

20% KOH Mount Microscopic Image Showing: 1a. Partially septate (blue arrow) right angle branching (black thick arrow), ribbon like folding (black thin arrow), 1b. Broad aseptate hyphae, 1c. Broad aseptate right angle branching hyphae 1d. Broad, partially septate, right angle branching hyphae, 1e. Aseptate, broad fungal hyphae (Black arrow), 1f. Aseptate hyphae

Figure 2

Imaging features of ROCM . (A,B) Black turbinate sign : an early sentinel sign of Ischemia and non-enhancement of turbinates in MRI scan, (C) CT axial image shows subtle increased density in intraconal fat in the right orbit, representing early inflammatory process, (D,E) showing orbital invasion and severe compromise of right nasal cavity and ethmoid cells in T1 fat contrast of MRI, (F) left sided Sphenoidoethmoiditis (G) left maxillary sinusitis with masticatory space inflammation, (H) left sphenoidal sinusitis with temporal dural enhancement, (I) loss of ICA flow void,

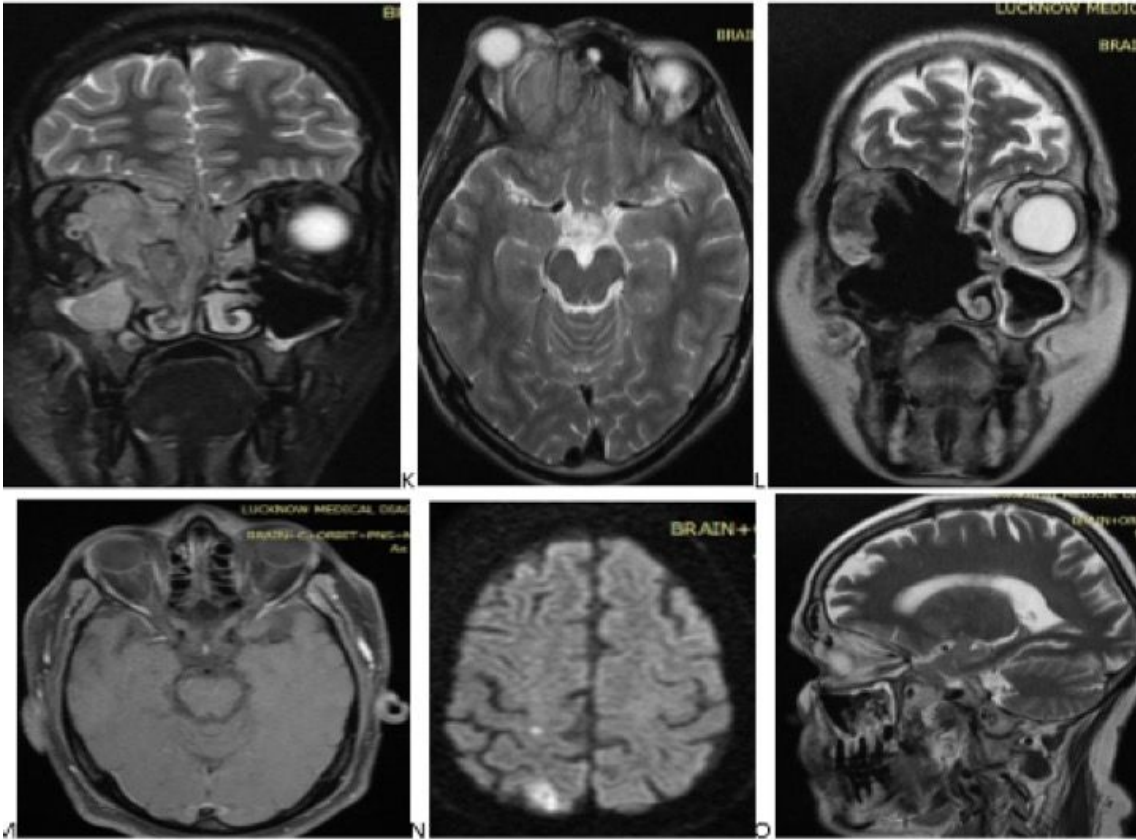


Figure 3

Imaging features of ROCM : (J)Inflammation of orbital tissues, right maxillary and nasal cavity, (K) R eye proptosis with orbital infiltration, (L) R eye exenterating with extensive sinus debridement state,(M) Bilateral temporal dural enhancement,(N) Infarct, (O)Fronto-maxillary sinusitis

Figure 4

Nasal Endoscopic Imaging revealed eschar over middle turbinate and slough over septum and medial wall of maxillary sinus 2a, middle turbinate 2b, nasal septum 2c.