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Comparative study of reliability of inflammatory markers over 18-FDG—PET CT scan in monitoring skull base osteomyelitis

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KEYWORDS
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Abstract
Introduction: The end point of treatment in skull base osteomyelitis is a matter of debate. A treatment based on symptoms alone is fraught with recurrence. There is a need to restrict imaging though more informative. The inflammatory markers like C-reactive protein and erythrocyte sedimentation rate used commonly need a detailed evaluation to optimize its utility.
Objectives: To compare the diagnostic accuracy of inflammatory markers with a hybrid PET scan in monitoring skull base osteomyelitis. The secondary objective was to obtain a cut-off value of these markers to decide upon antibiotic termination.
Methods: A prospective cohort study was conducted in a tertiary care center with fifty-one patients with skull base osteomyelitis meeting eligibility criteria. Patients diagnosed with skull base osteomyelitis were serially monitored with weekly markers and PET scan after the initiation of treatment. A hybrid scan was taken at 6–8 weeks of treatment and repeated if required. The follow-up period varied from 6 weeks to 15 months. The outcome measures studied were the values of markers and the metabolic activity of PET scan when the patient became asymptomatic and when disease-free.
Results: C-reactive protein and erythrocyte sedimentation rate had a statistically significant correlation to disease activity in PET tomography scan as a prognostic marker. Both showed good clinical correlation. A cut off value of $\leq$ 3.6 mg/L for C-reactive protein and $\leq$ 35 mm/hour for erythrocyte sedimentation rate were taken as normalized values.
Conclusion: A consistent normalized value of C-reactive protein and erythrocyte sedimentation rate for 8–12 weeks in an asymptomatic patient may be an indicator of disease control, though not cure. So, relying solely on markers alone for antibiotic termination may cause relapse. It may be used cautiously in a peripheral setting without access to more specific hybrid scans.

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In a tertiary care, follow-up scans may be done based on the titres, thereby limiting the radiation exposure.

Introduction

Skull base osteomyelitis (SBO), popularly known as malignant otitis externa (MOE) or necrotizing external otitis is a potentially fatal osteomyelitis of the skull base frequently affecting elderly diabetics.[1,2] The associated mortality which formerly was as high as 50%, has been significantly reduced in recent times with better antibiotic regimens and glycemic control. Though predominantly aural in presentation, central or atypical skull base osteomyelitis are also being reported.[3–6]

The diagnosis of SBO is mainly based on clinical features, culture, radiology, and histology.[2] Levenson's diagnostic criteria includes refractory otitis externa, severe nocturnal otalgia and purulent otorrhea associated with Pseudomonas infection and presence of granulation tissue in an immunocompromised or diabetic patient.[7–9] It is a well-known fact that erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) are elevated in SOB.[10,11] There are no guidelines for effective application of these markers to treat MOE. These values tend to be above the normal range even when patients become asymptomatic. Newer hybrid scans like FDG–PET CT and MRI are specific tools in the diagnosis and followup of SOB.[12] Other techniques have various drawbacks in diagnosing and monitoring SBO. High resolution contrast enhanced CT detects bone erosion when there is demineralization of 30% or greater. MRI, though good at soft tissue differentiation and detecting bone marrow edema, cannot assess response and resolution of disease.[13] Nuclear imaging modalities like technetium and gallium scan are good diagnostic tools, though poor spatial resolution is a drawback.[12,14] Tc-99 scan detects even a 10% rise in osteoblastic activity and hence detects osteomyelitis early. This is cheap and easily available. However, it shows positivity in conditions with a high bone turnover, as in the postoperative state or malignancy with bone involvement. It lags with clinical improvement, therefore, it cannot be adequately used in followup of treatment response. Gallium 67 citrate shows normalization with treatment response and hence used in treatment response monitoring. High cost and high radiation dose are drawbacks. Both these gamma tracers have low spatial resolution and lack anatomical detail. This is improved by beta emitters such as FDG.

The crux of treatment is systemic antibiotics for variable duration till symptoms abate.[2] The clinician is in a dilemma over the antibiotic choice, frequent switches and termination. Combination drug therapy along with cost of imaging modalities for diagnosis and followup take a financial toll on the patients.

Objectives

The primary objective of the study was to compare the diagnostic accuracy of CRP and ESR as prognostic factors in SBO when compared with 18-FDG–PET CT scan. The secondary objective was to achieve a numerical value for these markers as decision factors in antibiotic cessation.

Methods

The study protocol was reviewed and approved by the Institutional Ethics Committee of our institute (IRB-AIMS 2018–029). It was in accordance with the ethical standards laid down in the Declaration of Helsinki. All interventions and investigations were done with informed consent of the patient. A prospective cross-sectional diagnostic accuracy study was conducted for 24 months at a tertiary care center with an annual ENT outpatient load of approximately 30,000. Due to lack of similar studies a pilot study was conducted on 20 patients and the observations were used to design the present study. There was a total of 70 patients initially but some defaulted on followup. Finally, 51 patients were available for analysis.

Monitoring of CRP and ESR: SBO was diagnosed in patients with a history of refractory otitis externa, immunocompromised status, histopathology of granulation tissue if available, radiology and raised titres of ESR and CRP. Central SBO was diagnosed mainly with imaging and raised titers. In appropriate cases, workup was done to rule out other inflammatory conditions such as tuberculosis and collagen vascular disorders. Markers were monitored on a weekly basis for 6–8 weeks of treatment. The institutional normal range of CRP was $0-1$ mg/L and that of ESR was $8-20$ mm/hour. If the patient continued to be symptomatic (pain and ear discharge) at the end of 6–8 weeks, the markers were monitored monthly.

PET CT procedure: PET scan was generally done for all patients at the initiation and end of 6^{th} to 8^{th} week of treatment. For patients who reported with either CT or MRI taken elsewhere an additional diagnostic PET was not insisted upon, although all underwent PET at 6–8 weeks. GE Discovery PET CT machine performed the 18-FDG – PET CT. Patient was kept fasting for 4 h prior to the procedure and imaged by an integrated PET/CT camera, 45 min after injection of F-18 FDG (0.1 mCi $\times$ weight in Kg). An SUV (standardized uptake value) of 2.5 was taken as a cut-off to differentiate between malignancy and SBO. Values below 2.5 were considered inflammatory.[15] A morning blood glucose level between 80 and 150 mg/dL was taken as a safe range for scanning.

The report was given by a dedicated nuclear imaging specialist with special interest in this area. After an imaging at 6–8 weeks of treatment, repeat scan was performed every third month till it became metabolically inactive or earlier if the markers became normal or the patient asymtomatic. Additional CT or MRI was performed only if there were fresh symptoms.

Culture and antibiotics: Aural discharge or tissue sampling from granulations were cultured at the initial visit. While awaiting cultures patients were empirically started either on intravenous (IV) Ceftazidime (2 g per dose 12thhourly) or Piperacillin-Tazobactum (4.5 g 8thhourly) combined with IV or oral Ciprofloxacin (IV – 400 milligrams [mg] 12thhourly, oral 750 mg 12thhourly). If patient continued to be symptomatic after two weeks of initiation of antimicrobial therapy, deep tissue sampling was considered. Sampling sites included mastoid, clivus, greater wing of sphenoid, mandibular condyle, carotid canal, jugular foramen, eustachian tube and tympanic ring. Samples were routinely sent for histopathological examination and cultured for fungus, bacteria, and acid-fast bacillus. In those already on multidrug therapy a DNA-PCR with gene sequencing was done to improve the yield. When feasible a debridement with an aim to disease clearance without causing further morbidity was attempted during deep tissue sampling.

Antibiotics were given through a PICC line (peripherally inserted central catheter) for a minimum of 6–8 weeks duration. Treatment was generally stopped when PET became normal. If the patient remained symptomatic while on antibiotics and cultures were negative, antifungal medications were started. Empirical antifungal treatment was also given to patients who did not undergo deep tissue sampling. IV Voriconazole at a loading dose of 6 mg/kg 12thhourly for 2 doses followed by intravenous at 3 mg/kg or oral 200 mg 12thhourly as maintenance dose was given.

Statistical analysis was done using IBM SPSS statistics. Variables studies were the values of CRP, ESR, activity of PET scan and the symptoms of the patient during the treatment. To compare CRP and ESR with PET CT scan Mc Nemar Chi-square test was applied. Diagnostic validity parameters-sensitivity, specificity, negative, positive predictive values, and accuracy of CRP and ESR with respect to FDG – PET CT scan was calculated. An alpha level of less than or equal to 0.05 (p-value) was considered statistically significant.

Results

Out of the 51 patients, 27 patients had central SBO. The youngest was 45 years and oldest 88 years old. Demographic profile is given in Table 1. Pseudomonas Aeruginosa (21.6) was the commonest organism followed by Aspergillus species (11.8). Polymicrobial or no growth group accounted for 31.4%. Twenty-eight (54.9 %) patients underwent debridement.

At the end of 8 weeks of treatment, 30 patients were asymptomatic (Table 2). Of these, 28 had no metabolic activity on PET. Taking this as cure, the corresponding CRP and ESR were evaluated. Only 3 patients had reached institutional normal values of CRP and ESR. So, a cut-off value for normalcy was calculated for the markers using ROC curve

Table 1 Profile of the study population.

	n = 51	Percentage (%)
Gender		
Female	12	23.5
Male	39	76.5
Diabetes mellitus	48	94.1
Microbial flora		
Pseudomonas aeruginosa	11	21.6
Aspergillus species	6	11.8
Candida species	5	9.8
Staphylococcus aureus	2	3.9
No cultures/polymicrobial growth	16	31.4
Debridement	28	54.9

Table 1 showing male predominance (76.5%) and high association with diabetes (94.1%), Pseudomonas (21.6%) followed by Aspergillus (11.8%) and Candida (9.8%) were the main organisms.

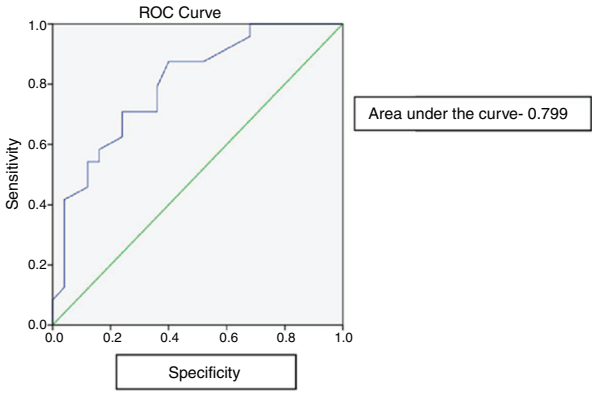

Figure 1 ROC curve showing good sensitivity and specificity for CRP.

(Fig. 1). The cut-off value for CRP was 3.6 mg/L with a sensitivity of 87% and a specificity of 60%, which was statistically significant with p = 0.002. Similarly, the cut-off value for ESR was 35 mm/hour which had a sensitivity of 83% and a specificity of 60% which was statistically significant with a p-value of 0.013 (Fig. 2). Of the 28 asymptomatic patients with negative PET, 17 reached the cut- off value of CRP and 16 for ESR. CRP had a specificity of 82.6% and a sensitivity of 60.7% and ESR had a specificity of 73.9% and a sensitivity of 57.1% when compared with PET as a prognostic marker, with an agreement of 70.6 and 64.7 respectively with statistical significance (Table 3). At the end of analysis of response of patients within 8 weeks of treatment, 30 patients were asymptomatic with no pain and discharge and stopped treatment. This included the two patients with positive activity on PET but with normalized markers. All these patients continued to be asymptomatic till the end of the study.

At the end of 8 weeks, the remaining 21 patients had positive activity (Table 2). They were further monitored though it was beyond the planned study period. Of these, 4 patients had normalized CRP and 4 had normalized ESR. Of these 21 patients, 9 stopped treatment within 6 months. Another four patients completed treatment within 15 months. Of the total 51 patients, 43 successfully completed treatment. Of the remaining 8 patients, while two patients relapsed,

Table 2 The titres of ESR, CRP, metabolic activity of PET CT and patient response with treatment. Showing the weekly titres of the markers and their relation to the metabolic activity of PET CT at the beginning of treatment and at the end of 6 weeks. The patient's symptom status at the end of study period (6 weeks to 15 months) is shown. Culture specific antibiotics given during the course of treatment is included.

S n°	Age (yrs)	Sex	Diagnosis	CRP						ESR						Initial PET activity	PET CT final	Culture	Medical management	Debridement/ Blopsy	Asymptomatic status/ Treatment status
Week1	Week2	Week3	Week4	Week5	Week6	Week1	Week2	Week3	Week4	Week5	Week6										
1	67	M	MOE	3.5	18	6.4	29	27	28	29	28	51	59	99	102	Not done	No	No growth	Itraconazole/ piptaz/ciplox	Yes	3 months
2	76	M	Central SBO	0.5	32	71	26	7	2	7	25	81	74	72	44	Yes	No	Aspergillus flavus	Inj fortum/ voricoazole/ ciplox	Yes	4 months
3	53	M	Central SBO	11	20	13	9	4	4	55	55	56	40	36	10	Yes	Yes	Klebsiella	Linezolid and vancomycin, magnex voriconazole, meropenem, minocycline	Yes	3 months
4	62	F	Central SBO	23	30	38	20	15	9	91	101	83	56	34	30	Yes	No	No culture	Ceftazidime, amikacin and metrogyl, IV magnex and oral linezolid and voriconazole, piptax and ciplox	Yes	6 weeks
5	65	M	Central SBO	24	117	68	23	21	14	107	108	113	108	97	50	Yes	No	No growth	Piperacillin, voriconazole	Yes	Lost for follow up
6	61	M	Central SBO	91	74	54	63	47	34	56	74	61	34	67	54	Yes	No	Aspergillus flavus	Voriconazole	Yes	5 months
7	64	F	Central SBO	13	10	9	4	3	2	19	52	54	43	40	38	Yes	Yes	Chryosporim, Pseudomonas acruginosa	Ceftazidime, voriconazole, ciprofloxacin, fluconazole	Yes	2 months
8	55	M	Central SBO	24	110	68	23	21	14	98	108	103	108	97	50	Yes	No	No culture	Ceftazidime	No	2 months
9	70	M	Central SBO	11	20	13	9	4	4	55	55	56	40	36	30	Yes	Yes	No culture	Piperacillin	No	Passed away
10	73	M	Central SBO	25	21	16	10	5	2	95	104	87	60	54	43	Yes	No	Candida para psilosis	Voriconazole, piperacillin, meropenem	Yes	6 weeks
11	45	M	Central SBO	24	21	15	8	3	1	67	80	57	65	45	14	Yes	No	Staph aureus	Voriconazole, piperacillin, clindamycin, cloxacillin, linezolid, ciprofloxacin	Yes	On antibiotics for 1 yr and a month, patient had symptomatic relief after 2 months

Table 2 (*Continued*)

S n°	Age (yrs)	Sex	Diagnosis	CRP						ESR						Initial PET activity	PET CT final	Culture	Medical management	Debridement/ Blopsy	Asymptomatic status/ Treatment status
Week1	Week2	Week3	Week4	Week5	Week6	Week1	Week2	Week3	Week4	Week5	Week6										
12	78	M	MOE	40	32	25	20	15	5	90	74	70	35	44	52	Yes	No	Pseudomonas, Candida Albinas	Ciprofloxacin and cefaperazone	No	2 months
13	60	M	Central SBO	0.7	3.6	4	4.2	3	3.3	70	96	103	97	88	58	Yes	No	Enterococcus fecalis	Ceftazidime, ciprofloxacin, piperacillin, linezolid, fluconazole	Yes	Lost for follow up
14	66	F	MOE	40	43	38	21	22	4	70	34	42	68	52	34	Yes	No	No growth	Ceftazidime, ciprofloxacin, voriconazole	No	Lost for follow up after 6 months IV and voriconazole
15	66	M	MOE	1.5	5.1	4	2.3	1.9	0,7	40	73	57	52	40	46	Yes	No	Gram negative bacteria	Piperacillin voriconazole, itraconazole	No	2 months
16	78	M	MOE	20	17	10	9	9.2	1	60	61	58	44	30	29	Yes	No	No growth	Ceftazidime	Yes	2 months
17	63	M	Central SBO	30	120	210	344	400	412	70	77	92	100	90	102	Yes	Yes	No growth	Piperacillin voriconazole, clindamycin	Yes	Antibiotics for 1 month, expired due to septic shock
18	77	M	MOE	6.5	16	22	30	32	23	54	44	40	36	28	18	Yes	Yes	Citrobacter kooseri, Klebsiella pneumoniae, enterococcus faecalis	Ceftazidime, ciprofloxacin	Yes	2 months
19	65	M	MOE	36	106	88	42	56	2	86	74	66	42	30	36	Yes	Yes	Pseudomonas aeruginosa	Ciprofloxacin, piperacillin	Yes	2 months
20	68	M	Central SBO	10	22	8.04	4	1.3	11	96	42	36	53	50	52	Yes	Yes	Candida hemulonii	Meropenem, voriconazole	Yes	6 months
21	72	M	Central SBO	47	79	13	31	26	23	96	107	97	90	88	80	Yes	Yes	Kodamea ohmeri	Cefaperazone, voriconazole, amphotericin	No	6 months
22	73	M	MOE	10	7.2	9.6	6	8	9.8	83	72	94	79		87	Yes	Yes	Pseudomonas aeruginosa	Cefaperazone, ciprofloxacin, piperacillin, voriconazole	Yes	4 weeks of piptaz and 4 months of voriconazole
23	59	M	MOE	23	20	16	10	4	2	74	55	42	33	20	28	Yes	No	No culture	Piperacillin, ciprofloxacin	No	6 weeks
25	62	M	MOE	11	6.1	5.5	10	17	19	49	45	36	51	59	64	Yes	Yes	Pseudomonas, Klebsiella, Streptococcus	Piperacillin, voriconazole	Yes	8 months of voriconazole and 3 months of piptaz

Table 2 (*Continued*)

S n°	Age (yrs)	Sex	Diagnosis	CRP						ESR						Initial PET activity	PET CT final	Culture	Medical management	Debridement/ Blopsy	Asymptomatic status/ Treatment status
Week1	Week2	Week3	Week4	Week5	Week6	Week1	Week2	Week3	Week4	Week5	Week6										
26	74	F	Central SBO	16	10	8	2	1.4	0.8	46	43	36	29	20	16	Yes	No	Aspergillus flavus	Voriconazole, cefaperazone, ciprofloxacin	No	2 months
27	72	M	Central SBO	20	16	12	8	4	2	51	50	40	44	35	38	Yes	No	No growth	Ceftazidime, ciprofloxacin, piperacillin, linezolid, fluconazole	No	2 months
28	64	F	MOE	31	15	34	98	108	9	81	46	42	44	34	20	Yes	No	Pseudomonas aeruginosa	Ceftazidime	No	6 weeks
29	61	M	MOE	7	16	18	15	93	1.3	50	61	76	85	53	25	Yes	No	Pseudomonas aeruginosa	Piperacillin, cefoperazone, voriconazole	Yes	3 months
30	71	M	Central SBO	43	13	6.5	6.07	5	3.2	69	81	68	40	42	38	Yes	No	No growth	Cefaperazone, ciprofloxacin	Yes	2 months
31	68	M	Central SBO	1.4	17	16	13	14.5	14	50	54	90	92	66	60	Yes	Yes	No culture	Voriconazole, linezolid	No	7 weeks of voriconazole
32	60	M	MOE	71	57	12.57	6.5	5.19	1.62	97	94	83	47	25	14	Yes	No	No growth	Piperacillin, meropenem	Yes	3 months
33	70	M	MOE	11.58	11.94	27	24	10	2.28	61	56	81	32	35	30	Yes	No	Candida non albicans (SG), Pseudomonas aeruginosa (SG)	Voriconazole, amphotericin B, doxycycline	Yes	2 months
34	80	F	MOE	9.3	19	5.79	10.85	9.9	8	90	69	88	17	62	60	Yes	Yes	No growth	Vancomycin, meropenem, voriconazole	No	10 weeks
35	63	F	Central SBO	8.59	11.19	10	9	6	5.6	97	30	32	40	20	18	Yes	No	No growth	Ceftazidime	No	6 weeks
36	70	F	Central SBO	17.68	24.46	67.31	50	46	30	37	57	60	48	32	50	Yes	Yes	Staphaureus (MG), Candida albicans	Ceftazidime, ciprofloxacin	No	Lost for follow up after 4 weeks
37	56	F	Central SBO	10	18.92	16	14	8.4	563	60	63	71	74	65	60	Yes	Yes	No culture	Voriconazole	No	4 months
38	54	M	MOE	4.76	4.7	11.5	11	16.8	4,3	37	47	57	47	30	36	Yes	Yes	Candida no albicans (MG)	Meropenem, voriconazole	Yes	6 months
39	62	M	Central SBO	10	7	5	3	11	9	46	47	44	38	42	40	Yes	Yes	Pseudomonas aeruginosa (MG)	Ceftazidime	No	2 months
40	75	M	MOE	3	2	54	15	2	0.93	23	23	30	27	10	5	Yes	No	Candida albicans	Ceftazidime	No	6 weeks

Table 2 (*Continued*)

S n°	Age (yrs)	Sex	Diagnosis	CRP						ESR						Initial PET activity	PET CT final	Culture	Medical management	Debridement/ Blopsy	Asymptomatic status/ Treatment status
Week1	Week2	Week3	Week4	Week5	Week6	Week1	Week2	Week3	Week4	Week5	Week6										
41	75	M	MOE	20	22	35	40	30	20	44	50	38	30	67	100	Yes	Yes	Aspergillus flavus, enterobacter sp.	Ciprofloxacin, cefaperazone	Yes	6 months
42	73	M	MOE	11	31	20	14	9.14	1.66	103	100	100	115	80	70	Yes	Yes	Invase aspergillosis	Ciprofloxacin, cefaperazone	Yes	2 months
43	71	M	MOE	8.38	17.26	22.4	20	15	13.2	30	80	54	40	60	76	Yes	Yes	No growth	Ciprofloxacin, ceftazidime	Yes	< 8 months
44	75	M	Central SBO	66	54	6.8	2.1	4	5	12	15	8	14	7	6	Yes	No	Pseudomonas aeruginosa (moderate growth), Staphylococcus aureus	Ciprofloxacin, cefaperazone	No	3 months
45	65	F	MOE	152	112	95	88	70	73	74	74	80	64	123	80	Yes	Yes	Aspergillus fumigatus	Cefaperazone, ciprofloxacin, voriconazole	No	Lost for follow up after 6 weeks
46	71	M	MOE	47	70	13	31	26	2	90	100	97	90	80	19	Yes	Yes	Staph aureus, ryosporium sp.	Voriconazole, terbinafine	Yes	6 months
47	70	F	MOE	4.76	4.7	11.5	12	16.8	4.3	60	50	52	38	32	24	Yes	No	Pseudomonas aeruginosa (scanty growth)	Ciprofloxacin, ceftazidime,	No	3 months
48	57	M	MOE	24.9	1,3	22.4	80.9	52	34	38	30	24	18	20	67	Yes	Yes	Pseudomonas aeruginosa (heavy growth)	Ceftazidime, piperacillin	Yes	Lost for follow up after 4 months
48	62	F	Central SBO	12	6.1	5.5	10	2.32	1.38	30	44	50	19	52	27	Yes	No	Pseudomonas aeruginosa, cryosporium	Ceftazidime, ciprofloxacin	Yes	2 months
50	69	M	Central SBO	31	13	34	98	108	10	81	42	42	44	34	20	Yes	No	Aspergillus flavus	Ciprofloxacin, cefaperazone, itraconazole	No	3 months
51	88	M	Central SBO	22.56					8.4	70					60		No	Pseudomonas aeruginosa	Ceftazidime, ciprofloxacine	No	3 months

Table 3 ESR and CRP profile at the end of two months.

Inflammatory markers		FDG–PET CT metabolic activity (n = 51)		*p*-value
Absent, n (%)	Present, n (%)			
ESR (mm/hr)	≤ 35	16 (57.1%)	6 (26.1%)	0.026[a]
> 35	12 (42.9%)	17 (73.9%)		
≤ 3.65	17 (60.7%)	4 (17.4%)	0.002[b]	
CRP	>3.65	11 (39.3%)	19 (82.6%)	

[a] Statistically significant correlation between ESR and metabolic activity in FDG PET at the end of two months.
[b] Statistically significant correlation between CRP and disease activity in FDG PET at the end of two months.

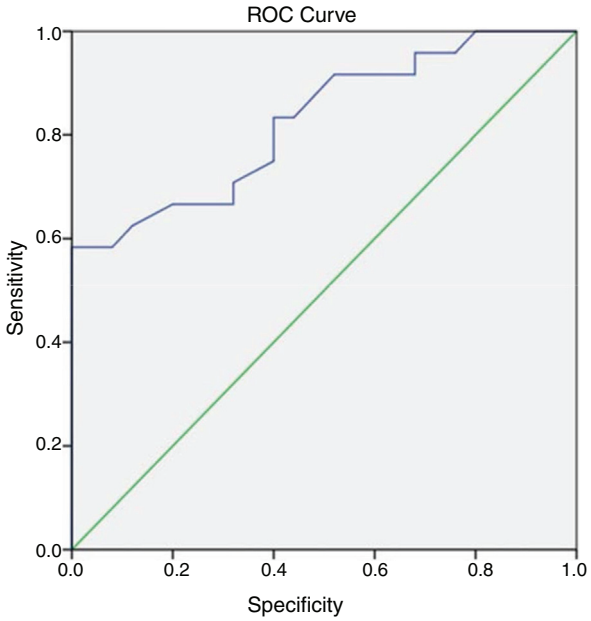

Figure 2 ROC curve of ESR.

another two succumbed to the long illness. Six patients were lost to followup at the end of 6 months of which half were asymptomatic with ongoing antibiotics waiting for the markers to stabilize. Readmissions were noted in four patients on Voriconazole with transaminitis and another two with relapse.

Discussion

Several studies including ours noted a sex distribution favoring male predominance. Because of the rarity of the disease, our sample size was small though comparable to others. We did not encounter pediatric osteomyelitis unlike Truck and Thompson et al. who described 2 cases affecting the clivus.[16] We had 48 diabetic patients. Shaun and Shyang et al. reported that 94.7% of their 18 patients were diabetics.[17]

In a study of 22 patients by Shaun et al., organisms were identified only in 63.2%. Nicholas et al. reported on 31 cases of SBO in which 61% grew Pseudomonas (49% were ciprofloxacin sensitive and 16% resistant) followed by Aspergillus species (10%). Ciprofloxacin monotherapy was the treatment of choice initially in SOB.[17] We had an almost equal number of pseudomonas and fungal growth (Table 1). Our patients received antifungals for 6 months to 1 year similar to Volsky study.[18] In view of high incidence of fungal organisms it is a point to ponder whether administration of long-term antibiotics led to secondary fungal infection. However, there is no available literature regarding this possibility.

Of the 51 patients, 23 were managed medically alone and 28 underwent some mode of surgical debridement (Table 2). Complete or near- complete disease clearance was possible only in twelve patients. Site and morbidity were key factors in limiting debridement in the remaining 16 patients. All the 12 patients with good clearance showed immediate improvement after the procedure. Some of them had a change of antibiotic post- procedure. Hence it is difficult to say whether the improvement was due to surgery alone. But clinically we felt that a complete surgical debridement cut short the treatment duration apart from yielding positive culture. However, in a study by Nicholas et al., only 3 patients out of the 18 underwent surgery with no improvement.[19] In Sang et al. study, 9 among 28 patients underwent surgery. He reported that intraoperative cultures did not yield additional information over ear swabs and disease persisted.[16] Our contrary experience included the two patients with intracranial debridement who recovered rapidly afterwards. It may be recommended to opt for complete debridement if feasible to shorten treatment duration. Khan et al. opined the need of surgical debridement when the treatment gets prolonged.[20] Shaun et al. described varying duration of antibiotics from 1 month to 6 months.[8] The Bone Infection Unit in Oxford, United Kingdom, recommended treatment of 6 weeks of intravenous treatment followed by 6–12 months of oral medication, guided by clinical response. Our patients received 6 weeks to 15 months of antimicrobials.

At the time of diagnosis both CRP and ESR were elevated in all cases. Those who responded showed relief of pain and discharge with trending down of CRP followed by ESR. The decrease in levels correlated with reduction of metabolic activity in PET scan. There was no literature available on SBO regarding this for comparison. There was no correlation with the extent of disease though clinically we felt clival lesions extending to both sides of the skull base were poor responders. Michail et al.'s study on diabetic foot osteomyelitis studied the usefulness of CRP, ESR, total count and procalcitonin as markers for activity.[21] They opined that these values could not be relied upon alone to predict outcome. All markers trended down with treatment but the continued elevated ESR was a pointer to ongoing osteomyelitis. Shaun's study reported total count as a better marker which was unlike

our observation where total count was normal for majority of patients.[16] Patients with disease that resolved after 6–8 weeks of intravenous therapy showed a 21.71% reduction in mean ESR values compared with the group with persistent disease, in which ESR values remained unchanged. A similar downward trend was also seen in CRP levels. None of our patients reached the institutional normal value of CRP and ESR when they became symptom- free or disease-free. But these patients reached the cut-off value for CRP ($\leq$3.6 mg/L) and for ESR ($\leq$35 mm/hour). Both were found to be statistically significant. ESR took longer to normalize. Since a similar study had not been conducted before no previous literature was available for comparison. These values could be taken as indicators to stop treatment. In our series, one asymptomatic patient had a rise in CRP and ESR after an unrelated surgical procedure. In our study, CRP had a specificity of 82.6% and a sensitivity of 60.7% and ESR had a specificity of 73.9% and a sensitivity of 57.1% when compared with PET. Though values were less it was statistically significant, and we found that it was significant clinically as well. It was particularly helpful to time the PET scan once the patient became asymptomatic.

At the end of 8 weeks, 17 of the total 30 asymptomatic patients reached the cut- off value of CRP and 16 reached the cut- off value of ESR. There was excellent correlation between inflammatory markers and PET CT. We found that CT and MRI were not reliable tools to assess response to treatment except to find new areas of involvement in case of development of fresh symptoms. Kroonenburgh et al. mentioned the disadvantages of CT and MRI over PET CT.[12] CT scan under- appreciates the soft tissue and intracranial structures besides its inability to distinguish infection from malignancy. Because normalization of bony changes may never occur despite resolution of the infection, CT is limited in tracking treatment response. MRI is usually not useful in monitoring the response to therapy in patients with osteomyelitis, because marrow changes caused by inflammation take 2–6 months to return to normal. As per Gherini et al. single photon emission CT improves the monitoring of therapy.[22] We did a PET CT at the end of 6–8 weeks for all patients and subsequently to monitor the progression of disease if required. There were 10 asymptomatic patients on intravenous antibiotics with PET CT showing persistent metabolic activity. CRP and ESR in these patients showed consistently stable values in the cut-off range showing that inflammatory markers can predict resolution of disease earlier than FDG – PET CT. A medical board from the departments of Otorhinolaryngology, Infectious disease control, Nuclear medicine, Neurosurgery and Microbiology discussed further action plan on these 10 patients and decided to withhold antimicrobials in those with normalized markers for more than 3 months with monthly monitoring of CRP and ESR and 3rdmonthly FDG – PET CT. Among these 10 asymptomatic patients in whom treatment was stopped based on a medical board decision, two had exacerbations. Another two showed no metabolic activity after almost a year. So, a consistent stable normalized value of CRP and ESR may indicate disease control though not cure. All patients with no metabolic activity on PET have remained symptom free to date, indicating cure. The observations pointed to a fact that SBO patients while on antibiotics showed a predictable pattern of becoming asymptomatic first followed by normalized CRP and then normalized ESR followed by hybrid scan. The treatment has to continue in an asymptomatic patient till the PET scan becomes normal or till the inflammatory markers show stable normalized values.

During the course of the study a treatment pattern evolved which we followed. Culture specific antibiotics (if available) were given preferably as combination therapy for a minimum of 6–8 weeks in a patient with a positive response. With poor response the earliest attempt would be made for deep tissue sampling. Antifungals were initiated in symptomatic patients with no culture and not responding to the empirical treatment. We did observe that generally non-responders were fungal SBO. Antifungals required a longer duration from 6 months to one year or more compared to antibiotics. We now terminate antibiotics in a patient who is clinically asymptomatic with a negative PET scan at the end of 6–8 weeks. If the scan continued to show activity after prolonged treatment, antibiotics were stopped when the inflammatory markers reached and stabilized at the cut -off value of $\leq$ 3.6 mg/L for CRP and $\leq$ 35 mm/hour for ESR for at least 8–12 weeks. This was based on our observation of 10 asymptomatic patients with stable markers but active PET scan. Such patients were monitored monthly to watch for rising titers and PET every 3 months.

Our observations may be used with some caution in low resource setting where there is no access to hybrid imaging. In a tertiary care facility, this helps to time the imaging to decide upon termination of antibiotics. Repeat imaging may be done if the inflammatory markers have stabilized for 8–12 weeks. The sample size was limited due to the rarity of the disease and long duration of follow up required. A similar study utilizing PET MRI with its superior functional assessment, spatial resolution and of course less radiation is required.[23] The study population with multiple combination therapies may have acted as confounding variables.

Conclusion

CRP and ESR are reliable tools for detection, progression and resolution of disease status as compared to PET CT in SBO. The lesser specificity of the markers may limit their use as the sole indicator of resolution of disease. Nevertheless, they can be used effectively, repeatedly, and economically to time hybrid scans during the course of the disease to decide upon antibiotic termination. This study may be utilised to evolve a treatment guideline in the management of SBO.

Ethical statement

The study protocol was reviewed and approved by the Institutional Ethics Committee of our institute (IRB-AIMS 2018 – 029). It was in accordance with the ethical standards laid down in the Declaration of Helsinki. All interventions and investigations were done with informed consent of the patient.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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