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Primary Ewing's Sarcoma of Mandible: Treatment with Combination Therapy and Microvascular Reconstruction: A Case Report

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Abstract
Introduction: Ewing's sarcoma (ES), is a type of small round cell lesion of Neuroectodermal origin and depicts as a malignancy of bones that majorly affects children and younger adults. The tumor has a predilection for male and white people. Clinically when seen, this tumor represents an aggressive type of behavior thereby more chances of micro metastasis during diagnosing the disease. Oral ES is an infrequent tumor entity which can mimic odontogenic inflammation, hence proper clinical, radiological and histopathological diagnosis methods should be incorporated.
Case Report: We present a report of ES in a 12-year young boy with chief complain of continuously growing mass in right back side of mandible. OPG revealed a characteristic moth eaten appearance and biopsy revealed round cell tumor.
Conclusion: The following case report presents a novel technique as treatment modality for Ewing's sarcoma with satisfactory and efficient results.
Index Terms: Ewing's Sarcoma, Inflammation, Malignant, Neuroectodermal origin

I. INTRODUCTION

ES is a true malignancy with poorly differentiated and biologically aggressive tumour[1], introduced in 1921. Recently, electron microscopic and immune-histochemical analysis differentiated this tumour under a group of non-epithelial neoplasms of neuroectodermal type and ES being sixth most common and lethal malignancy of small round cell tumour of soft tissues and bone and is of neurogenic origin.[2] The World Health Organization has linked the disease as ES/Primitive Neuroectodermal Tumour, on a criteria that both the groups represent same process and that they share the same genetic alteration (translocation 11:22) in over 95% of the cases.[3]
It constitutes 10–20% of malignant tumours [4] and second most common malignant bone tumour that occurs in young children (1% of all malignant tumours) [5] and young adults with other types of round cell tumours including, Ewing family of tumours (ESFT), rhabdomyosarcoma, lymphoma, neuroblastoma and desmoplastic round cell tumours and fourth most occuring bone malignancy which presents in children after myeloma, chondrosarcoma and osteosarcoma.
The ES Family includes: Ewing's sarcoma of the bone, Extraosseus Ewing's sarcoma, PNET, Peripheral neuroepithelioma, Atypical Ewing's sarcoma and Askin's tumor.

The tumour presents specifically in males in proportion of 2.1-2.4:1, affecting the age group of Range: 1-43 years, mean age is 15 years and 3 months and is ten times more present in Caucasian children rather than black children.[6, 7]

Ewing Sarcoma (ES) is most commonly found in the long bones of body (58%), pelvis region (20%) and ribs (7%).[8] Head and neck region ES is less frequent accounting for 69% in Mandible, 28.2% in Maxilla and 2.8% in Soft tissues: representing about

3% of all cases and affecting less frequently in the maxilla with 10.5% of all primary tumours of the mandible.[9] Approximately 34 % of the Ewing's Sarcoma (ES) patients exhibit metastasis as both distant metastases like bone marrow metastasis and metastases of regional lymph node as pulmonary metastasis, Patients showing lung or pulmonary metastasis show better outcomes in comparison to bone or bone marrow metastasis. The five-year survival is 76% for child less than 15 years and it is 60% for young adults aged between 15 and 19 years. Survival also depends on other factors like how far is the spread of tumor. The overall 5-year survival percentage for people of all age groups with ES is 62%.

Genetically, Ewing sarcoma has "*cluster of differentiation 99*" (CD99) type of protein encoded by the Myc2 gene located on the short arm of chromosomes X and Y it is highly sensitive for small blue round cell tumors in children. An accurate diagnostic shows presence of translocation "t(11;22)(q24;q12)", in 80-90% of cases [10] leading to formation of a *fusion gene* called *EWS/FLI1 (Ewing Sarcoma/Friend leukemia integration 1 transcription factor)*. In 5% cases, other translocations, "t(21;22)(q12;q12) and t(7;22)(p22;q12)", producing fusion genes *EWS-ERG and EWS-ETV1* can be found and one-fourth part of tumors present "p16 and p53" alteration too, depicting the tumor of more aggressive behavior and showing poor response to therapy.

II. CLINICAL AND RADIOLOGICAL FINDINGS

Patients with Ewing's Sarcoma (ES) presents clinical local symptoms like swelling indicating induration, pain, venous dilation, hyperemia and tumor mass formation. Due to bone metastasis pathological fractures may also occur and spinal metastasis-associated back pain can also lead to spinal paralysis.

Hematological and serum examinations reveal anemia and leukocytosis, increased ESR, raised serum level of LDH,[7] alkaline phosphatase, and CRP which are commonly similar symptoms seen in any inflammatory disorder leading to differential diagnosis of osteomyelitis.

Radiographically, plain radiographs exhibit infiltrative damage of the affected part of bone which appears as onion skin describing periosteal reactions. Disease is often confirmed by upgraded radiological investigations like CT scan for ruling out extraskeletal mass of soft tissue, damage to bone cortex, and pulmonary metastasis. MRI plays a vital role in showing low intensity on T1-weighted and high intensity on T2-weighted images, as extraskeletal soft tissue masse are derived from bone. High 99mTc-MDP uptake on bone scan and 18F-FDG uptake on PET scan is also used.[9]

III. CASE REPORT

A 12 year boy reported to OPD with chief complaint explaining gradual increase in swelling on the right part of face involving mandible since 2 months with mild associated pain.

On clinical examination, an extra oral facial asymmetry (Figure 1A, B) due to a diffuse increasing swelling was seen on right part of lower jaw extending superiorly up to ala tragus line, anteroposteriorly at right commissure of the mouth till pinna region of right ear involving both body and angle of the mandible with no secondary or sensory changes with a measurement of about 4*5 cm. Intra oral examination (Figure 1C) revealed swelling involving right canine to second molar tooth region, with significant bicortical expansion of right mandible covered with normal mucosa on Bi-digital palpation with, no perforation. No relevant past medical/dental history was present.

After palpating the consistency of swelling was painless and firm. Absence of discontinuity was seen in inferior border of mandible. Lymph node examination revealed enlarged, solitary, fixed, unilateral and firm and hard in consistency left submandibular lymph node.

CT scan was done to exactly locate anatomical relation of the tumor, which further revealed osteolytic lesion in right mandibular body and ramus with sunburst appearance with significant soft tissue matrix enhancement and cortical breach in 1st and 2nd molar region (Figure 2A, B). A biopsy of lesion collected as marginal section of right mandible reflected tumor cells in cluster, with features suggestive of small blue round cell tumor which can be a) Neuroblastoma or b) Ewing's sarcoma (Figure 2C).

A multilevel oncology based evaluation was performed to establish individual treatment protocols. IHC examination of section showed positive presence for neural markers such as for CD99, FLI-1, negative for SATB2 (ruling out Osteosarcoma) and vimentin positivity was observed favoring diagnosis of PNET/Ewing's sarcoma.

PET CT scan (Figure 3 A, B, C) done to characterize lesion showed Fluoro-deoxyglucose
(FDG) avid lesion in right hemi mandible with primary mitotic pathology involving bilateral cervical lymph nodes as well, confirming with clinical and radiological investigations the diagnosis of Ewing's sarcoma involving right hemi-mandible.

IV. TREATMENT MODALITIES SO FAR

Until now treatment provided for ES is broadly divided into 3 categories which include chemotherapy, radiotherapy and surgery depending on size of tumor. Poor or complete negative response to chemotherapy, age of patient (>15 years), positive CD133 and KI-67 (KI-67 reactivity >50%) which can be linked with poor prognosis and reoccurrence for ES , and thereby following combinations are practiced:

a) Chemotherapy
b) Chemotherapy, surgery followed by radiotherapy
c) Surgery and radiotherapy
d) Surgery and chemotherapy
e) chemotherapy and radiotherapy

f) chemotherapy and surgery

If tumour is considered difficult to remove with an adequate healthy margin, then a preoperative radiotherapy involving 36–55 Gray (Gy) is considered first. A postoperative radiotherapy is performed when the margin removed after surgery is not sufficient for local control.

1960s	"A group of 60 patients with localized primary ES of bone from January 1981 until April 1985 showed better prognosis with smaller tumours treated with local control following radical surgery as before this radiotherapy was the mainstay of treatment".
1980s	"Since year 1964, a group of 66 patients with primary ES were treated with local radiotherapy of the primary site in combination with adjuvant regimens of intensive chemotherapy. An alkylating agent and a vinca alkaloid were used with alternating high-dose of Adriamycin and cyclophosphamide-vincristine".
(Nesbit ME Jr, 1990)	"The Intergroup ES Study included a group of 331 patients, where the prognosis of patients treated with the VAC regimen and VACD regimen were compared and 60 % survival rate was seen with VACD regimen".
(1988–1992) (Grier HE,2003)	"The evaluation of single VDC-containing regimen versus VDC+IE regimen was done and VDC + IE had a significantly positive effective on patient survival in localized cases".
(R. B. Womer, D. C. West, 2008)	In 856 patients randomization was done: 6 VIDE + 1 VAI + 7VAC(n = 431) +7VAI (n = 425) "Chemotherapy for Ewing sarcoma was re-established in the early 2000s with five drug regimen resulting in better prognosis than three drug regimen and that every two-week cycle was superior to conventional timing of every three week cycles".
(Meyers et al., 2001)	"5 cycles of induction chemotherapy was done which included high-dose of melphalan, ETO, and whole body irradiation after stem-cell support".
(Schuck et al., 2003)	"For local control in poor responders to chemotherapy after wide resection, postoperative radiotherapy was done".
(Akiyama T, 2010)	"Fibula strut grafts or Non-vascularized fibula grafts along with other reconstructive options were considered".
(Sorin T,2014)	"A macro plate and a cement spacer were used for the reconstruction of right horizontal mandibular branch as an Induced membrane".
(Grevener et al. 2016)	"It has been well established that ES treatment should begin with induction chemotherapy followed by local control of the disease. The optimal local treatment strategy (surgery and/or radiotherapy) remains controversial".

Treatment:

- In view of localized primary pathology (Ewing's sarcoma) to right hemi mandibular bone with sparing of the other lymphatic regions, following management plan was decided: (Figure 4).

1. Presence of occult micro metastatic disease in patients with ES, the Induction chemotherapy for at least 12 weeks before the local therapy is preferred. Our treatment in the report included **neoadjuant chemotherapy** to:

- increase the chances of complete resection with microscopic negative margins and reduction in tumour size
- and destroying potential occult micro metastasis,
- Some bone healing occurs during Chemotherapy
- Diminish the risk of pathological fracture.

According to NCCN guidelines 2019, for Ewing's sarcoma following drug regimen is recommended:
First line therapy comprise of:
VDC/IE alternate with ifosfamide and etopside
VAI
VIDE (vincristine, ifosfamide, doxorubicin, etopside)
It comprised EVERY 3 WEEKLY FOR 4 CYCLES GIVEN of treatment with a three drug regimen which were Vinblastine, Cyclophosphamide and fluorouracil (VEF), actinomycin D and CPM (VAC regimen) along with administration of GCSF in pegylated form at 19 weeks. After neo-adjuvant chemotherapy imaging studies (PET scan) for chemotherapy response assessment was done to evaluate reduction in the tumor size in order to allow complete removal and use of anti-tumour drugs for postoperative chemotherapy (Figure 5 A, B).

2. **Local therapy** was a key factor including surgical treatment, due to the continuous growth of the facial bones and soft tissues of young patient. The detrimental effects of surgery on nutrition and deglutition, speech, vision, respiratory system and facial esthetics were also kept in mind.

Factors which determine incorporation of local therapy are

- Initial location & resect ability,
- Functional Capacity,
- Increased morbidity,
- Risk of secondary malignancies with late onset in high dose RT exposed tissues,
- Patient selection and,
- Primary response of tumor to chemotherapy.

Post NACT patient had non-metastatic local lesion with good clinical outcome to CT. To remove the malignant tissue with 2 cm of surgical margins and to reconstruct the resulting defect, a segmental resection of right side including the body of mandible was performed. Bony marrow and bone scrapings sent for frozen section for microscopic negative margin status. The bony defect was then reconstructed using Non-vascularized fibula graft and titanium reconstruction plate. The use of post-operative radiotherapy is dependent on the histological effects of chemotherapy and surgical margin of the resected tissue. As suggested by literature, "After adequate wide excision and to those who respond well to preoperative chemotherapy, in such cases radiotherapy is not indicated". (Figure 6 A-F)

3. Immediate administration of intensive chemotherapy is important in ES, so maintenance (adjuvant chemotherapy) is recommended following local control treatment and the duration of chemotherapy should be between 48-49 weeks with VAC-IE regimen alternatively for weeks. (Figure 7 A, B, C)

V. DISCUSSION

The outcome of ES has developed immensely in past years due to better understanding of pathology and improved diagnostic measures e.g., molecular techniques that focus on detecting characteristic fusion genes with immunohistochemical techniques and conventional histological.

Carbon ion beam treatment in past years has gained popularity for locally controlling surgically inaccessible areas of tumour because of variations in anatomy which also increases the quantity of dose of anti-tumour drugs by their bi-weekly administration, causing better prognosis of patient. New drugs are becoming accessible leading to further increase in patient survival rate such as pazopanib, [7] eribulin, [8] and trabectedin.[10]

VI. CONCLUSION

ES is a combination of characteristics of radiological, histological and specific clinical features. In-depth analysis and long-term follow-up is important for early diagnosis. ES is a very uncommon malignancy that affects the facial bones of children. This case report highlights the facial outcomes and findings of different radiographic modalities for the diagnosing this malignancy. Any type rapidly spreading swelling in children with ulcerated appearance should be evaluated keeping in mind Ewing's sarcoma as a differential diagnosis. All doctors should have knowledge about the radiographic findings and clinical appearance for diagnosing disease as early as possible due to its tendency to metastasize and poor prognostic outcome.

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VIII. LIST OF ABBREVIATIONS

1) ES- Ewing's Sarcoma
2) WHO- World Health Organization
3) PNET- Primitive Neuroectodermal Tumor
4) ESFT- Ewing Family of Tumor
5) CD99- Cluster of Differentiation 99
6) Myc 2 Gene- a Proto-oncogene
7) EWS/FLI1- Ewing Sarcoma/Friend leukemia integration 1 transcription factor
8) EWS-ERG and EWS-ETV1- oncoproteins of Ewing's sarcoma
9) LDH- lactate dehydrogenase
10) CT- Computed tomography
11) MRI- Magnetic Resonance Imaging
12) MDP- Methyl diphosphonate
13) FDG- Fluoro-deoxyglucose
14) IHC- Immunohistochemistry
15) SATB2- specific immunohistochemistry marker
16) KI-67- nuclear protein that is associated with cellular proliferation
17) VDC/IE- vincristine, doxorubicin, cyclophosphamide, Alternate with ifosfamide and etopside
18) VAI- vincristine, doxorubicin, ifosfamide
19) VIDE- vincristine, ifosfamide, doxorubicin, etopside
20) IFO- an alkylating agent
21) ETO- a vinca alkaloid
22) GCSF- Granulocyte colony-stimulating factor
23) NACT- Neo-Adjuvant Chemotherapy
24) RT- Radiotherapy

IX. ACKNOWLEDGEMENT

Dr Vikas K. Singh – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Dr Ruchika Tiwari – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Dr Gaurang Thanvi – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Dr Hetvi Saxena– Acquisition of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

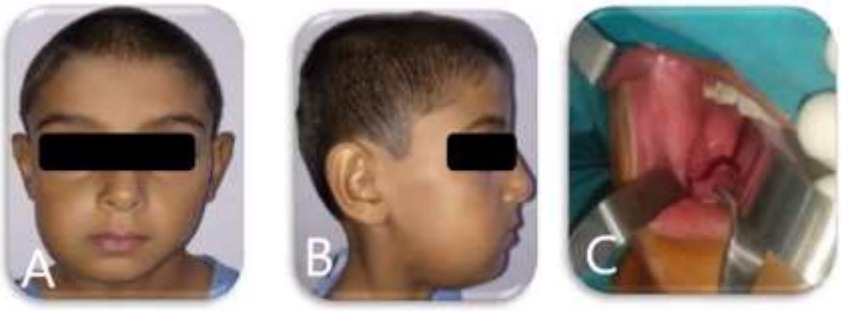

Figure 1: A, B- Preoperative extra oral Image, C- Preoperative intra oral images

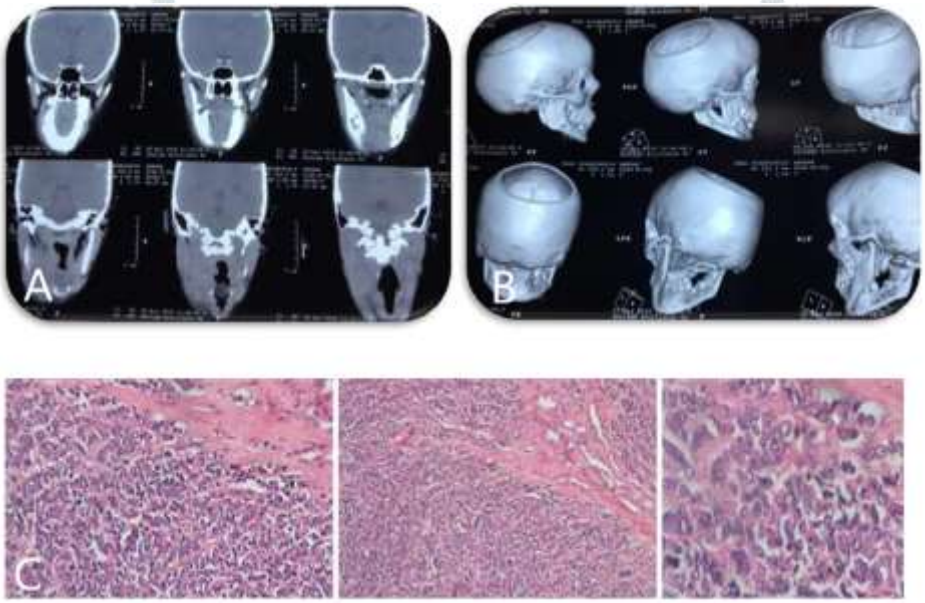

Figure 2: A, B- CT Scan, C- HPE examination

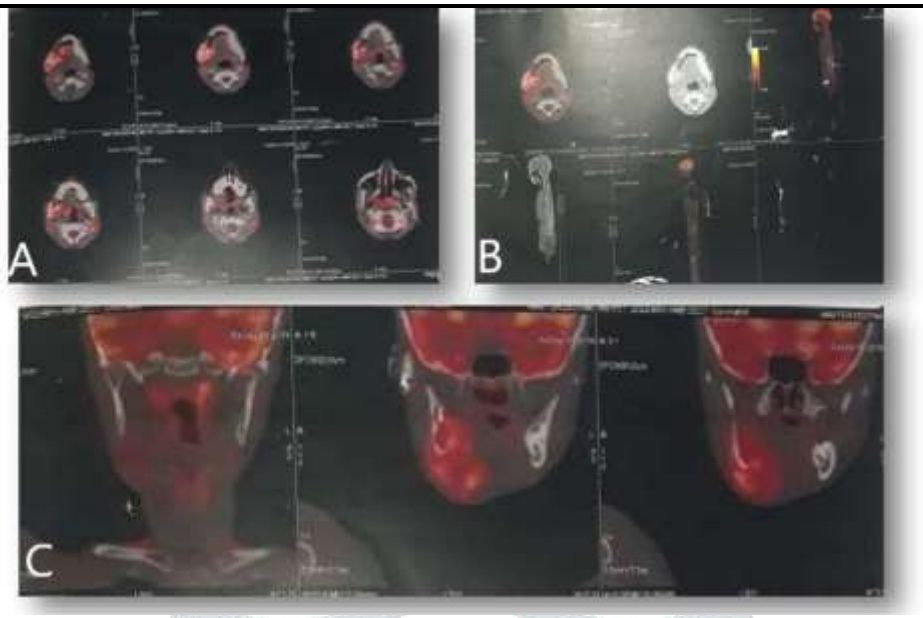

Figure 3: A, B, C- PET scan images

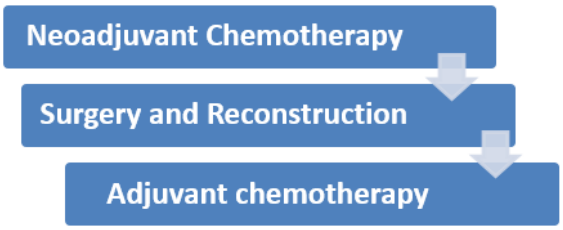

Figure 4: Treatment Options

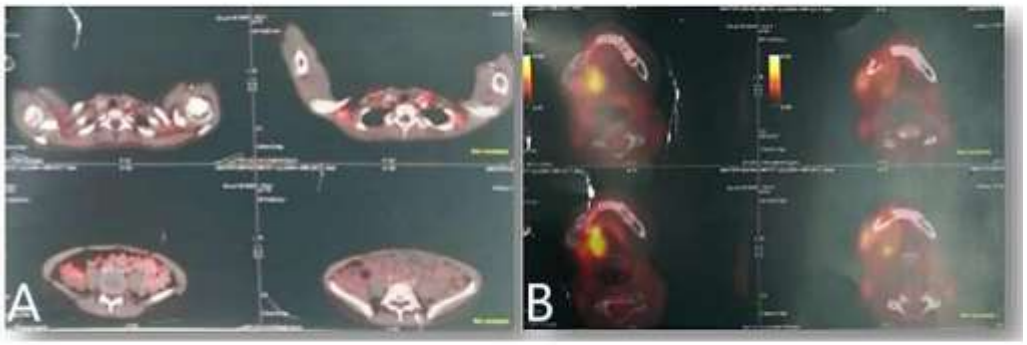

Figure 5: A, B- PET CT post chemotherapy

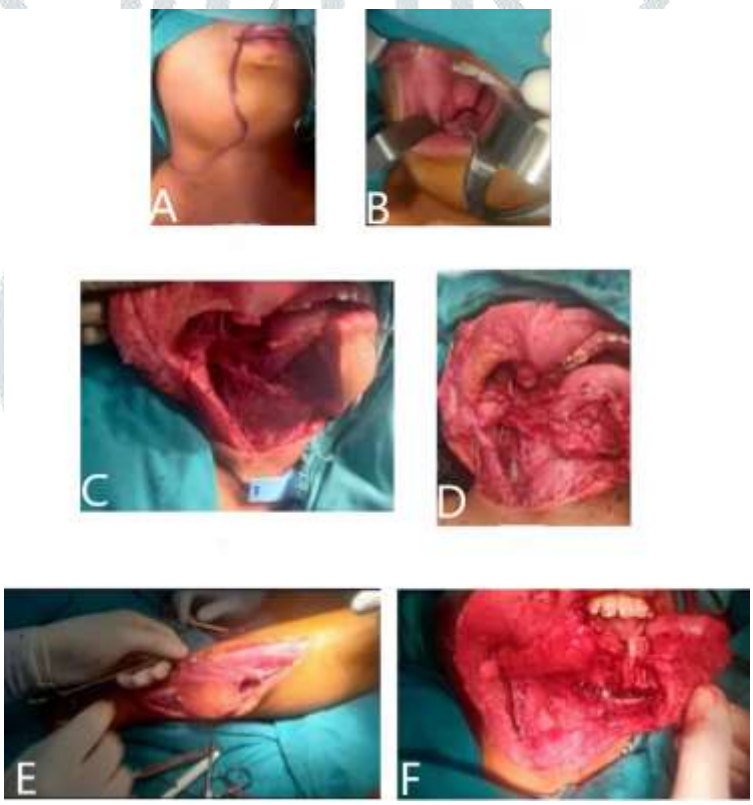

Figure 6: Intra operative images: A-D- incision, exposure and resection, E- fibula graft harvest, F- fixation with titanium Reconstruction plate

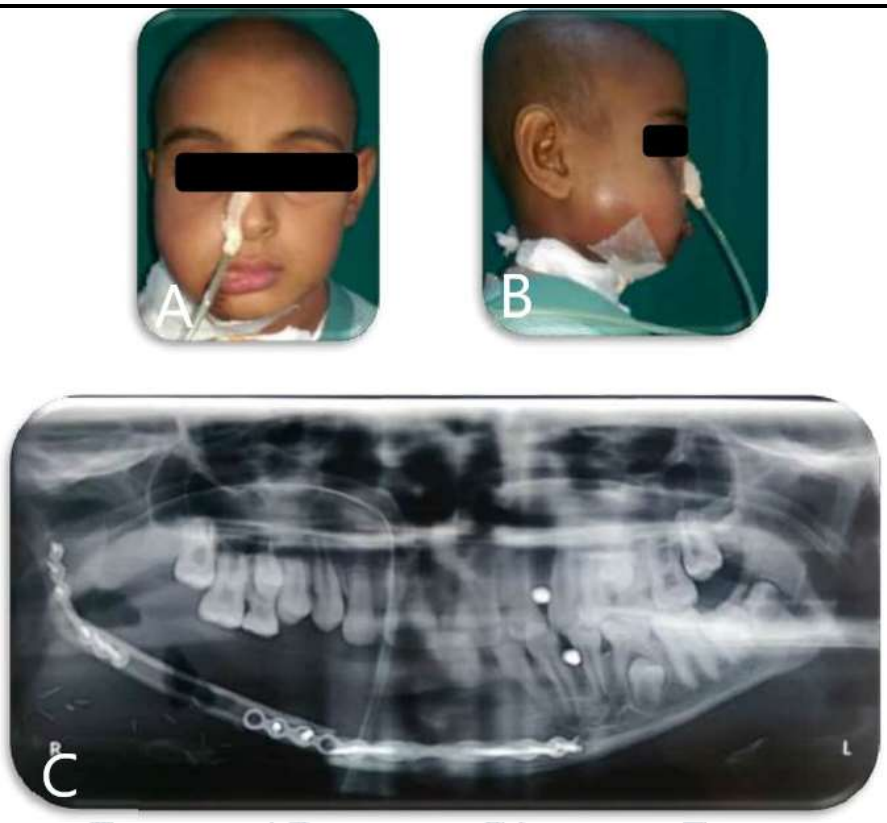

Figure 7: A, B, C- Post-operative clinical and radiographic images