Successful Outcome of Disseminated Candida Tropicalis Osteomyelitis on Remission Induction for Childhood Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia - Case Report

Lichun Xie
Jinan University First Affiliated Hospital https://orcid.org/0000-0002-6183-5904
Qingling Long
Shenzhen Children's Hospital
Guichi Zhou
Shenzhen Children's Hospital
Si-xi Liu
Shenzhen Children's Hospital
Feiqiu Wen (fwen62@163.com)
https://orcid.org/0000-0001-5559-633X

Case report

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Abstract

Background: Invasive fungal infection (IFI) is one of the most challenging complications in children with acute lymphoblastic leukemia (ALL) treatment, but acute fungal osteomyelitis (OM) is rarely encountered.

Case presentation: Here, we describe a case of Candida tropicalis osteomyelitis in a 10-year-old patient with Philadelphia chromosome (Ph)–positive ALL. He was on remission induction therapy at the time of neutropenia, and abscess developed in the right arm. The blood and bone cultures were positive for Candida tropicalis. Antibiotics and anti-fungal were given. A magnetic resonance of the arm revealed in intraosseous abscess, suggestive of OM. Surgical irrigation and debridement of the bone were performed immediately. The patient was effectively treated with antifungal therapy and ALL treatment. Now he full recovered into complete clinical remission but with sequelae visible by Magnetic Resonance Imaging (MRI). He took oral posaconazole for consolidation until disappearance of the lesion shadows on MRI and received subsequent cycles of chemotherapy in parallel.

Conclusions: In the successful management of Ph-positive ALL, dasatinib the second-generation Abl–tyrosine kinase inhibitor is crucial. The recommended treatment for candida osteomyelitis in Ph-positive ALL patients are fungicidal agent combined with surgery and modification chemotherapy with dasatinib. Using combined modalities of treatment seem to be crucial in the successful management of Ph-positive ALL.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy (1). Children with ALL are immunocompromised patients who are at high risk of infection associated with high morbidity and mortality rate (2). Invasive fungal infection (IFI) is one of the most challenging complications in children with ALL treatment (3), but acute fungal osteomyelitis (OM) is rarely encountered. In immunocompromised children the most common mechanism of these complications includes fungal osteomyelitis due to continuous infiltration or hematogenous spread (4). Candida species are weak pathogens that are common commensal organisms inhabiting the skin and mucous membranes of most individuals. However, the rate of incidence of invasive candidal infection is increasing (5). How to successful management of fungal osteomyelitis and chemotherapy of ALL is quite difficulty. Here, we report a case of childhood Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia, complicated by disseminated candida tropicalis osteomyelitis of the right humerus during remission induction and successfully managed by timely and appropriate administration without compromising antileukemic therapy.

Case Description

A 10-year-old boy was confirmed diagnosis of Philadelphia chromosome (Ph)–positive ALL. According to the Chinese Children's Cancer Group study ALL-2015 (CCCG-ALL-2015), he was provisionally assigned to

the intermediate-risk based on his presenting clinical features and immunophenotype, and philadelphia chromosome–positive ALL. He received upfront window therapy with dexamethasone for 4 days followed by remission induction with prednisone acetate, vincristine, daunorubicin hydrochloride (DNR), and pegaspargase from days 5 to 28.

He began to receive dasatinib (80 mg/m^2 per day) as soon as the diagnosis was made on day 5 of remission induction. On day 18 of remission induction, he was hospitalized for cough, fever and pain, tenderness and swelling over the right elbow. Laboratory tests were notable for neutropenia and elevated inflammatory markers (Fig. 1). Computed tomography (CT) scan chest showed pneumonia. The right upper limb ultrasound revealed swelling of soft tissue, without previous trauma. Empiric treatment with broad spectrum antibiotics was initiated to cover both gram positive and gram negative bacteria. The lesion progressed to an abscess in the upper right arm. 22 h later, blood culture show fungus positive and pus amphotericin B. Minimal inhibitory concentrations indicated susceptibility to amphotericin B (minimal inhibitory concentration <=0.5 μg/mL), fluconazole (1) and voriconazole(0.125) and flucytosine (<=0.4). He subsequently developed pain and swelling over the right upper arm and forearm. Five days after admission, he was afebrile, but pain, edema, limited function of the right elbow was progressive. Repeated ultrasound revealed discrete paraosteal edema adjacent to the humerus one week after admission. Magnetic resonance imaging (MRI) of the right humerus showed an intraosseous abscess and probable osteomyelitis (Fig. 2). Surgical irrigation and debridement of the bone were performed immediately (Fig. 3). Culture of bone aspirates obtained during surgery also was identified as candida tropicalis sensitive to amphotericin B, the same results with blood culture. Smear study of the bone fragments gathered during the surgery revealed fungal spores. All chemotherapy including except prednisone acetate was withdrawal for one week. Debridement was repeated on the third postoperative day, followed by significant improvement of clinical and laboratory findings. His condition improved. One week later, when he was non-toxic, hemodynamically stable, non-haematopoietic toxicity and inflammatory markers remained within the normal range, induction therapy was continued with some modification was continued with prednisolone and dasatinib, and treatment was carried out for osteomyelitis with amphotericin B, meropenem and vancomycin in parallel. Successful control of osteomyelitis was achieved by serial surgical debridement of lesion, antibiotics, amphotericin B and HBO therapy. Treatment with amphotericin B was administered for a total of 3 weeks, during which time he regained the ability to move the arm, and transitioned to oral posaconazole for consolidation, which he is currently receiving on an ongoing basis. Vincristine (D19 and D26), and L-asparaginase (D26) were administrated until the fever was brought under control and neutrophile granulocyte (ANC) ≥ 500/mm3. After completion of remission induction therapy he achieved complete remission (CR). After that, we put off the remission induction treatment consisted of cyclophosphamide (CTX), cytarabine (Ara-c), and mercaptopurine (6-MP) from days 29 to 35. The next chemotherapy was continued with dasatinib, weekly Vincristine and daily mercaptopurine for 3 weeks. Subsequent cycles of chemotherapy were reinitiated as per the protocol. On follow up 5 months later, the patient continues to do well.

Discussion And Conclusions

Candida organisms are found in the skin, respiratory tract, vagina and stools. According to the multicenter study in Australian (6), Candida species accounted for the majority of infections in association with neutropenia in immunocompromised patients with ALL, of which Candida albicans and C. parapsilosis were most frequently detected. According to another retrospective study, the proportion of candida is increasing in children with ALL (7). To our knowledge, there is rarely report of candida tropicalis osteomyelitis in a child with ALL. Predisposing factors present in our case were underlying leukemia, steroids, neutropenia, and immunosuppressive therapy, which is consistent with the research (8).

Proving a diagnosis is the first key step to the successful in management of IFI. Isolating and identifying the causative fungus on culture is important for epidemiological and research purposes. The culture of biopsy specimen is more sufficient than blood to demonstrate pathogen helps to establish the diagnosis as quickly as possible.

A combination of early diagnosis, surgical debridement and antifungal therapy seem to be crucial. The timely administration of empirical amphotericin B on suspicion of fungal infection in our case along with debridement of necrotic tissue may be responsible for a successful outcome.

In the successful management of Ph-positive ALL, dasatinib the second-generation Abl–tyrosine kinase inhibitor is crucial. According to our randomized clinical trial, dasatinib at a dosage of 80 mg/m^2 per day yielded superior results in the treatment of Ph-positive ALL (9). Anti-infection combined with surgical incision and drainage, and dasatinib administration, which together led to the successful treatment of osteomyelitis while maintaining a remission state of Ph-positive ALL.

The importance of judicious concomitant administration of antifungal and anti-leukemia treatment during induction therapy in ALL is highlighted. Moreover, we highlight the most efficient diagnostic and treatment strategies for fungal osteomyelitis with ALL is the combination of medical and surgical management. When there is significant marrow toxicity and infection for patient Ph-positive ALL, the concurrent myelosuppressive agents such as DNR, Ara-C, CTX, MTX, 6-MP should be stopped instead of dasatinib. It can be an effective treatment option for patients who need both infection control and ALL treatment.

List Of Abbreviations

ALL (acute lymphoblastic leukemia)

Ara-c (cytarabine)

CCCG-ALL-2015 (Chinese Children’s Cancer Group study ALL-2015)

CT (computed tomography)

CR (complete remission)

CTX (cyclophosphamide)

DNR (daunorubicin hydrochloride)

IFI (Invasive fungal infection)

OM (osteomyelitis)

Ph (Philadelphia chromosome)

ANC (neutrophile granulocyte)

MRI (Magnetic Resonance Imaging)

6-MP (mercaptopurine)

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Shenzhen Children's Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Written consent to publish this information was obtained from the parent of the study participant.

Availability of data and materials

The microarray data will be available in NCBI database.

Competing interests

We declare that we have no financial and personal relationships with other people or organizations that may inappropriately influence our work.

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Authors' contributions

XLC designed data analysis and wrote the manuscript; Qingling Long and Guichi Zhou provided imaging assistance; Sixi Liu and Feiqiu Wen contributed to critical revision. All of the authors have read and approved the manuscript.

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Figures

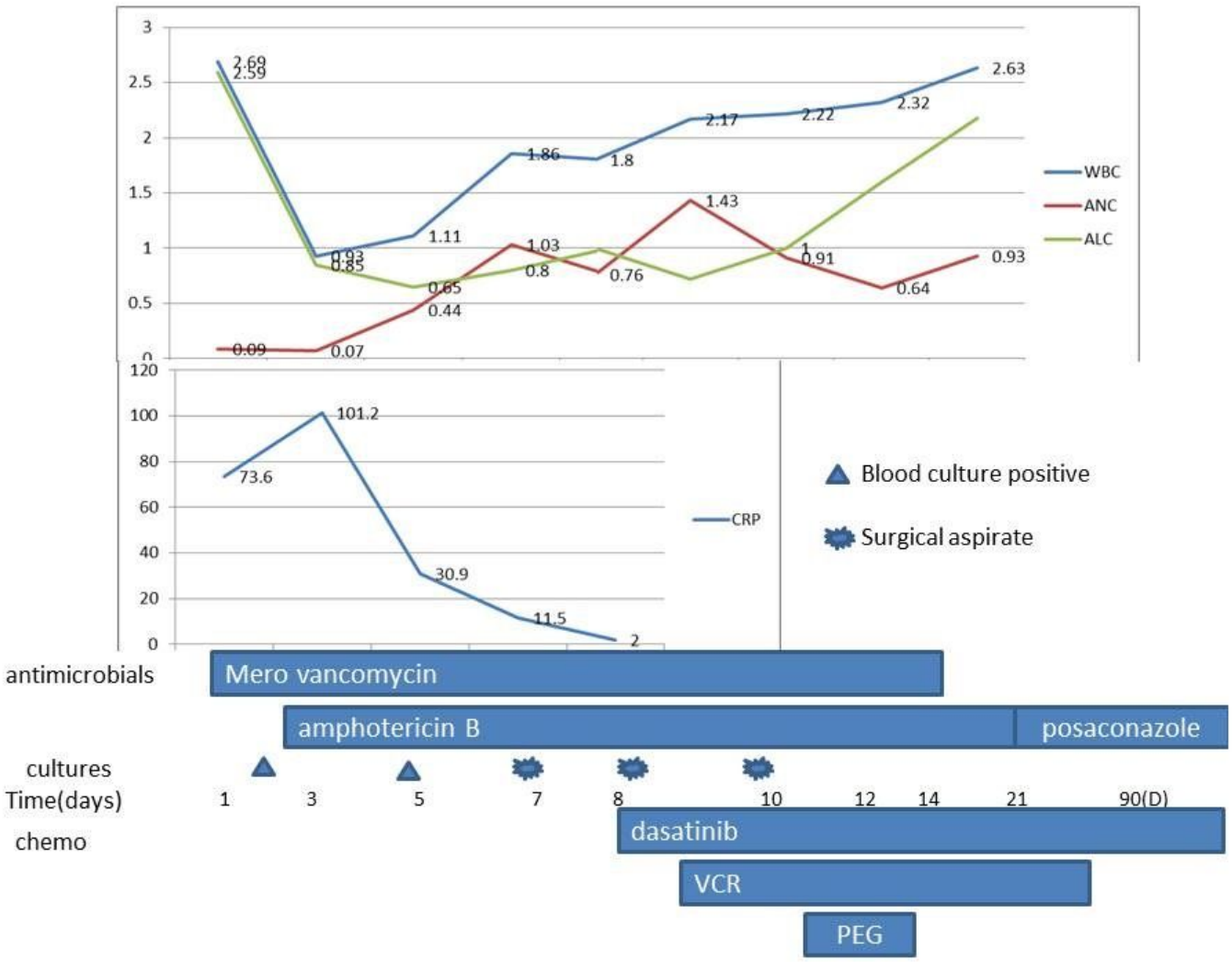

Figure 1

The result of Laboratory test, antimicrobial treatment and chemotherapy.

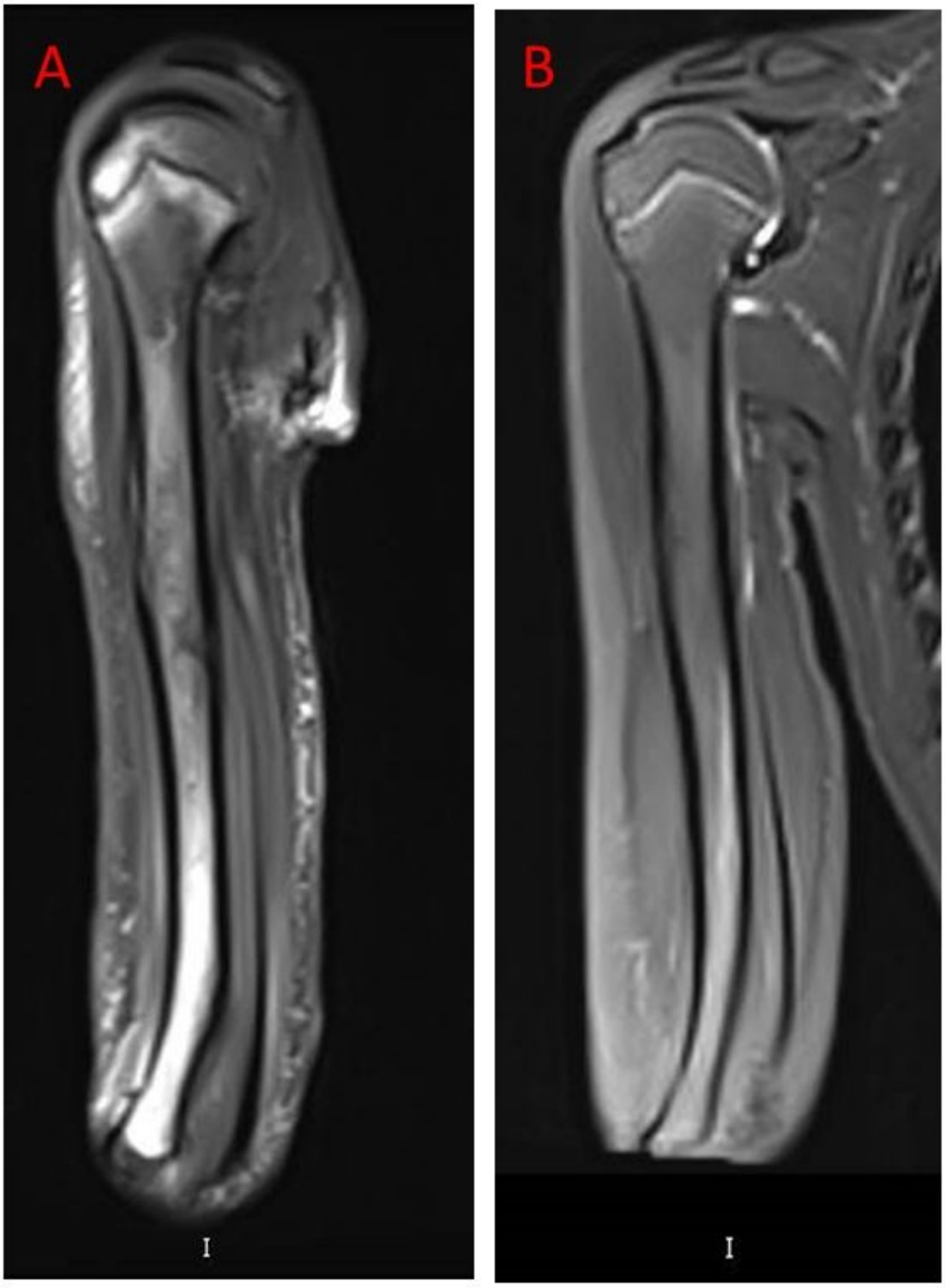

Figure 2

The MRI images of the right arm at first (A) and follow-up MRI, the previous abnormal signals narrowed significantly (B).

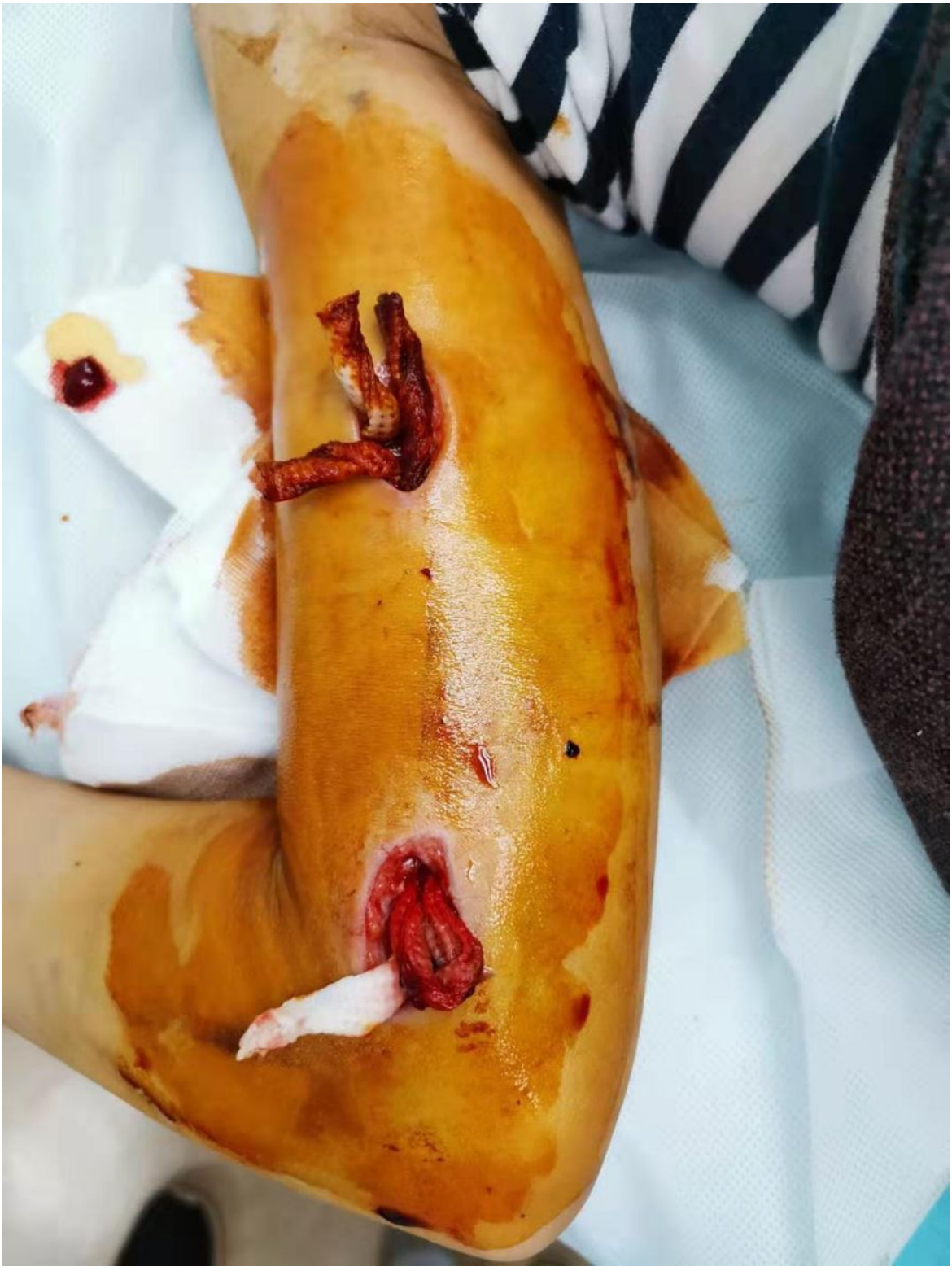

Figure 3

Surgical irrigation and debridement of the bone.