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Case Report

A Successful Application of NGS-guided Precision Medicine in Ewing Sarcoma in Iran: A Case Report

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Abstract

Background: Ewing sarcoma is a rare, aggressive malignancy of bone and soft tissue, primarily affecting adolescents and young adults. Even with access to standard chemotherapy and radiotherapy, patients with metastatic or recurrent Ewing sarcoma, particularly in lower-resource settings, continue to experience limited survival outcomes.

Case Presentation: We report the first known use of Next Generation Sequencing (NGS) testing to guide individualised treatment for Ewing sarcoma in Iran. A 17-year-old male presented with a paraspinal tumour and rapid neurological decline. Following surgical resection and histopathologic confirmation of Ewing sarcoma, he received standard chemoradiotherapy. Genomic profiling, including Tumour Mutational Burden (TMB) and circulating tumour cell immunocytochemistry, was conducted to identify precision therapeutic options. The patient's TMB was low (2 mutations/Mb), pMMR and MSI-low, ruling out immunotherapy candidacy. However, VEGFR1/2 expression supported the inclusion of Sorafenib. A customised regimen combining oncology and repurposed non-oncology agents was initiated. After seven treatment cycles, imaging revealed resolution of lung metastases and a reduction in spinal involvement, accompanied by significant functional recovery.

Conclusion: This case illustrates the feasibility and clinical significance of integrating molecular diagnostics into the treatment of rare cancers in low-resource settings. Even when immunotherapy is excluded, precision medicine can offer novel pathways to disease control and improved outcomes.

Keywords: Ewing sarcoma; Precision oncology; Tumour mutation burden; VEGFR; Pharmacogenomics; Iran

Introduction

Ewing sarcoma is an uncommon but highly aggressive neoplasm that primarily affects bones and soft tissues in children and young adults. First described by James Ewing in 1921, this tumour is notorious for its rapid progression and tendency to metastasise early. It frequently involves the long bones, pelvis, and thoracic wall; however, extraosseous forms also exist. Early diagnosis of Ewing sarcoma is often delayed, as it can present with symptoms resembling trauma or benign musculoskeletal injuries, leading to initial misdiagnosis or under-evaluation.

Advancements in chemotherapy, surgery, and radiotherapy have improved outcomes for localised disease. However, patients with metastatic or recurrent disease continue to face dismal survival rates. These challenges are magnified in Low and Middle Income Countries (LMICs), where access to advanced diagnostics and targeted therapies remains limited. In response to these challenges, molecularly guided therapy is gaining attention as a strategy to personalise treatment and optimize outcomes in rare malignancies, such as Ewing sarcoma.

Next-Generation Sequencing (NGS), which enables comprehensive profiling of somatic mutations and molecular alterations in tumour DNA, is increasingly recognised as a critical tool in precision oncology. While NGS-derived biomarkers have shown promise in predicting responses to certain systemic therapies, their primary value lies in identifying actionable targets in rare malignancies, such as Ewing sarcoma, where standard treatment options are limited. In this report, we present the first documented case in Iran where NGS, in combination with immunocytochemistry, was used to guide an individualised treatment plan for a patient with metastatic Ewing sarcoma.

Case Presentation

A 17-year-old male presented with acute lower extremity paraesthesia and gait imbalance. His symptoms rapidly progressed over days to include paralysis, bowel and bladder dysfunction. The patient had no consanguineous family background, and his only familial cancer history was a second-degree relative treated successfully.

MRI revealed a 55 × 43 × 50 mm mass in the right paravertebral musculature at the L3-L4 level. Surgical resection *via* neurosurgical intervention achieved near-total removal of the lesion, which extended into the epidural space.

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Histopathology sections revealed uniform, undifferentiated cells with scant cytoplasm arranged in islands separated by fibrous strands. Individual cells showed Inconspicuous nucleoli (Figure 1).

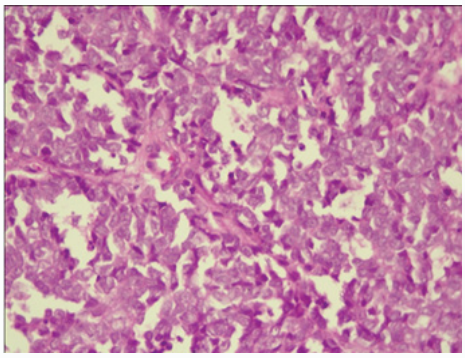

Figure 1: Microscopic image of a Haematoxylin and Eosin (H&E)-stained section from a Formalin-Fixed, Paraffin-Embedded (FFPE) tissue block.

According to radiology and morphological findings, several differential diagnoses were considered for this patient, with Ewing Sarcoma at the top of the list. Therefore, a limited Immunohistochemistry Panel (according to available markers) was ordered for this patient. IHC markers showed strong membranous CD99 staining and focal positivity for NSE. Other markers, such as LCA, CK, S100, Synaptophysin, and Chromogranin, were negative.

As the next step to confirm the diagnosis of Ewing sarcoma, FISH for t (11;22) was needed, which was not available in our centre. Since the patient was a very good Candidate for targeted therapy, an NGS panel that also covered the EWSR1-FLI1 fusion was performed for him.

One month after surgery, follow-up imaging demonstrated bilateral pulmonary nodules (4 mm - 9 mm) consistent with metastases (Figure 2). A whole-body bone scan indicated focal uptake in the lumbar vertebrae.

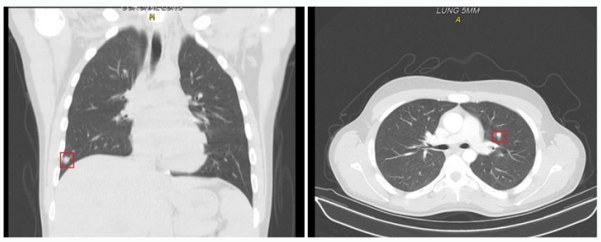

Figure 2: Multiple nodules are evident in different cuts of the lung CT scan.

Radiotherapy was initiated alongside biweekly vincristine. Upon completion of 25 fractions, systemic chemotherapy commenced according to the Lanzkowsky protocol, which involved alternating cycles of vincristine, Cyclophosphamide, doxorubicin, and Ifosfamide with etoposide.

After the first cycle, the patient developed vincristine-induced neuropathy, confirmed by EMG/NCV. Vincristine was discontinued.

To guide further treatment, tumour tissue and blood were sent for comprehensive genomic profiling. The Tumour Burden (TMB) was reported at two mutations/Mb, below the threshold for immunotherapy benefit. Immunocytochemistry of circulating tumour cells showed positive expression of VEGFR1 and VEGFR2, suggesting potential benefit from anti-angiogenic therapy.

Based on the molecular findings and treatment tolerability, a tailored combination regimen was developed, consisting of the following agents:

1. Sorafenib 200 mg daily
2. Atorvastatin 60 mg daily
3. Celecoxib 100 mg twice daily
4. Curcumin daily
5. Monthly Zoledronic Acid 4 mg IV

These agents were administered in combination with ongoing chemotherapy.

Due to neuropathy caused by vincristine, that drug was omitted from his protocol.

Outcomes

After seven treatment cycles, re-evaluation included spiral chest CT, spinal MRI, and whole-body scan. Pulmonary nodules had resolved completely.

Bone scan revealed reduced uptake in the lumbar spine, with no new lesions. Neurologically, the patient demonstrated partial motor recovery in the lower extremities, accompanied by improved ambulation and independence in daily activities. Compared to the last CT scan, the previous pulmonary nodules have been resolved at the present time, indicating a complete response to the treatment (Figure 3).

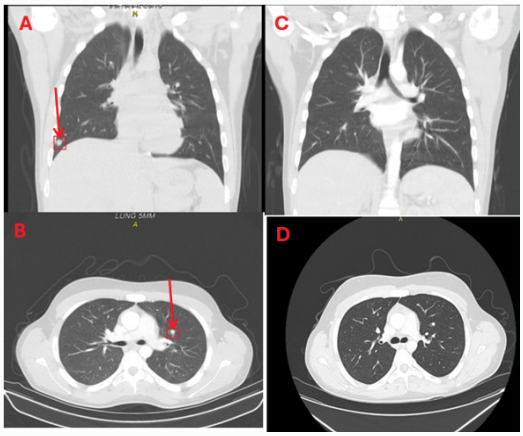

Figure 3: Resolution of the nodules found on Pre-treatment CT scan; (A&B: CT chest before treatment, C&D: CT chest after completion of the 7th Cycle of individualised treatment.

Discussion

This case illustrates how precision medicine can be effectively applied, even in resource-constrained settings where treatment options are often limited. Our patient's journey with metastatic Ewing sarcoma serves as a potent reminder: Each complex diagnosis affects not only the patient but also their family and care team, all of whom must work collaboratively to navigate limited treatment pathways and explore individualised options.

Ewing sarcoma remains a formidable diagnosis, particularly

in its metastatic form. For practitioners worldwide, including in our context, the prognosis for such cases is often bleak, and access to personalised care remains limited [1-4]. Yet, recent advances in molecular diagnostics, such as Tumour Mutational Burden (TMB) assessment and immunocytochemistry, are beginning to shift this paradigm. These technologies offer new avenues for targeted treatment, even in resource-constrained environments [2,5].

In this patient's case, the path to a tailored regimen began with a thorough molecular characterization of the tumour. Low TMB and negative PD-L1 expression ruled out the use of immunotherapy. However, the detection of VEGFR1/2 positivity created an opportunity for targeted anti-angiogenic therapy [6]. In this instance, the molecular profile directly influences treatment choices, allowing us to avoid options that are unlikely to be effective and focus on a biologically rational regimen [5,7].

What distinguished this case was not just the use of targeted agents, but the deliberate and evidence-informed combination of repurposed drugs, chosen not only for their individual merit, but also for their synergistic potential:

- **Sorafenib:** An anti-angiogenic agent, was selected for its inhibitory effects on VEGFR1 and VEGFR2. Its role in disrupting tumour vasculature may also improve chemotherapy delivery and overcome resistance.
- **Celecoxib and Curcumin:** Both targeting the COX-2 pathway, were combined to modulate tumour-promoting inflammation. Preclinical data suggest their synergy enhances apoptosis and reduces tumour progression.
- **Atorvastatin:** Typically used for dyslipidaemia, was included for its anti-proliferative effects and ability to potentiate anti-angiogenic therapy.
- **Zoledronic Acid:** While providing skeletal support, may also exhibit direct anti-tumour effects, particularly valuable in cases with bone involvement.

The combined therapeutic strategy yielded measurable outcomes; Following seven cycles of the combined treatment, the lung metastases resolved, and the spinal lesions regressed. These outcomes reflect the benefits of integrating targeted therapy, drug repurposing, and clinical responsiveness tailored to the patient's evolving condition [1,2,8-10].

Beyond the molecular and pharmacologic strategy, this case is defined by its human context-a teenager facing paralysis, a devoted family, and a responsive care team. The journey was fraught with challenges, including treatment-related neuropathy, but also underscored the importance of adaptability and shared decision-making. Modifications to the regimen were made to balance efficacy with quality of life, demonstrating the principles of truly patient-centred care [2,4].

Collaboration was central to the success of this approach among the medical team, across disciplines, and between established evidence and emergent therapies. Ongoing communication between the medical team, patient, and family was instrumental in adapting treatment and managing complications throughout the care process.

While this case presents a compelling narrative of hope, it also underscores the pressing need for expanded research and improved access to molecular diagnostics and innovative treatments. The synergy observed here must be validated in broader studies, and its lessons disseminated, particularly to under-resourced settings where they could have the most significant impact [1,4].

Conclusion

This is the first documented case in Iran where Next-Generation Sequencing (NGS) and pharmacogenomic profiling directly informed the management of Ewing sarcoma. The favorable response to a tailored regimen combining conventional and repurposed agents shows how NGS-based treatment strategies can be feasibly implemented to inform treatment decisions in low-resource clinical settings. Future efforts should focus on the broader implementation of this approach and its validation in larger cohorts.

Ethical Approval

Informed consent was obtained from the patient and their family for all diagnostic and therapeutic procedures, as well as for publication purposes. The ethical code is designated as IR.SUMS.MED.REC.1404.125 was obtained from Shiraz University of Medical Sciences.

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