Molecular characterization of interdigitating dendritic cell sarcoma

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Abstract

Interdigitating dendritic cell sarcoma is an extremely rare cancer that lacks a standard treatment approach. We report on a patient who was surgically resected and remains disease-free. The tumor was assessed for druggable targets using immunohistochemical staining to identify potential agents that could be used in the event of disease recurrence.

Case Report

A 25-year-old woman presented with a solitary enlarged right axillary lymph node. Prior medical history includes hyperreninemic hypertension, without an identified pathologic lesion, requiring angiotensin receptor blockade medication one year before the cancer diagnosis, and a sinus infection requiring antibiotic therapy immediately before the cancer presentation. The patient initially noted a nontender swelling under her right axilla and sought further medical evaluation. Upon completion of antibiotics for the sinus infection, the patient underwent an ultrasound and excisional biopsy of a 2×1 cm enlarged right axillary lymph node with clear margins. Patient's family history negative for blood disorders or malignancy and she denied tobacco or alcohol use.

Figure 1 shows the tumor stained with hematoxylin and eosin (H&E). Additional immunohistochemistry staining (IHC) was performed. The tumor specimen was strongly positive for S100 in majority of cells, MelanA negative, and smooth muscle actin was moderately positive in the majority of tumor cells. A bone marrow biopsy revealed normocellular marrow with adequate trilineage hematopoiesis, and markedly decreased iron staining; normal karyotype, 46 XX. Flow cytometry revealed no monoclonality, evidence of lymphoma or leukemia. The final pathologic diagnosis was interdigitating dendritic cell sarcoma (IDCS) after independent confirmation at a reference pathology laboratory (performed by RJP).

[18F]-2-fluoro-deoxy-D-glucose (FDG) computed tomography (PET/CT) revealed low uptake of FDG tracer in right axilla in area of excision. No adenopathy was visualized. The patient was followed conservatively without receiving adjuvant chemotherapy or radiotherapy.[1] Follow-up PET/CT scans at 4, 7, 11, 18, and 24 months showed no evidence of disease recurrence and physical exam was stable and remained unremarkable. She is now followed conservatively on an annual basis with physical examination and imaging.

Using a molecular profiling approach, we assessed her tumor for potential treatment targets to see if there would be conventional[2] or investigational agents under development that could be used to treat her cancer in the event of disease relapse. Only formalin-fixed, paraffin-embedded (FFPE) tumor was available. IHC molecular characterization for treatment targets was performed (TargetNow® test, Caris Life Sciences, Phoenix, AZ, USA)[2] with potential treatment options shown in Table 1. The tumor was positive for SPARC, secreted protein acid rich in cysteine (Figure 2), and HSP90 (Figure 3) and negative for PDGFR, MSH1, MSH2, c-kit, Her2/Neu, P-glycoprotein, ER, PR, Androgen Receptor, CD25, and CD52. Of note, the tumor sample was also sent for commercial testing for carcinoma unknown primary (CUP) testing to see if it had a molecular signature in common with up to 39 cancer types (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, USA). The sample was run twice, and remained "unclassifiable" amongst the list of 39 cancer genomic signatures. The closest matches for this patient's tumor, albeit with low probability, were B-, T-, and Hodgkin's lymphoma, small cell lung cancer, and melanoma.

Discussion

Interdigitating dendritic cells are potent antigen presenting cells found in T-cell areas of peripheral lymphoid tissue.[3] IDCS is an extremely rare neoplasm that can mimic other primary and metastatic spindle cell neoplasms of lymph nodes. Characterized by S100, CD68, and CD45RB staining, IDCS often presents with metastasis and portends a poor prognosis.[3] Within localized disease treated with surgery alone, approximately 50% remain disease-free with a median follow up of 12 months (range 2 months to 19 years).[1] In contrast, with advanced IDCS, survival rarely exceeds 12 months, despite various treatment modalities including surgical excision, multiagent systemic chemotherapy and/or radiotherapy.[3] Here we present molecular characterization of a case of IDCS with oncogenes identified as potential targets for treatment.

One of the targets identified was SPARC, also known as osteonectin. This protein belongs to a family of matricellular proteins and there has been growing evidence of its role in a variety of cancers.[4] High levels of SPARC could be targeted by nanoparticle albumin-bound (NAB)-paclitaxel, approved for use in patients with metastatic breast cancer and currently undergoing Phase III trials for patients with pancreatic cancer (*www.clinicaltrials.gov*). A few studies indicate that SPARC over-expression improves the response to the anticancer drug, nab-paclitaxel. It is thought that improved response is related to the high affinity of albumin to SPARC, thus will potentiate nab-paclitaxel to specifically target SPARC expressing cells.[5,6] The other target identified was HSP90 (heat-shock protein 90). This is an evolutionarily conserved chaperone molecule that is involved in the folding, stabilization, activation and assembly of various client proteins.[7] Cancer cells often require higher HSP90 activity to maintain their malignant potential, thus HSP90 has emerged as a promising therapeutic target. Indeed, there are several intravenous and oral formulations of HSP90 inhibitors in various phases of drug development (*www.clinicaltrials.gov*), though no HSP90 therapeutics are currently commercially approved for cancer treatment at this time.

In summary, this patient had localized IDCS, treated with surgical excision, and remained disease free at at least 24 months without requiring any adjuvant therapy. IDCS is an

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Table 1. Immunohistochemistry staining analysis-interdigitating dendritic cell sarcoma.

Positive IHC staining	Conclusions	Specificity	Intensity	%	Potential agent to be tried
SPARC	Positive	Specific	3+	40	Paclitaxel-albumin bound
HSP90	Positive	Specific	2+	70	HSP90 inhibitor (e.g. CNF2024, SNX5422, IPI-504, or a geldanomycin derivative)

Other IHC proteins tested but not considered targets due to absence of 2+ IHC in ≥30% of tumor cells include: PDGFR, MSH1, MSH2, c-kit, Her2/Neu, P-glycoprotein, ER, PR, Androgen Receptor, CD25 and CD52. IHC, immunohistochemistry staining.

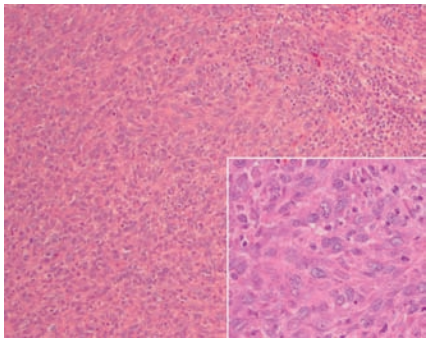

Figure 1. Interdigitating dendritic cell sarcoma tumor Specimen-hematoxylin and eosin stain at 10X magnfication. Higher magnification (40X) is displayed in lower right quadrant.

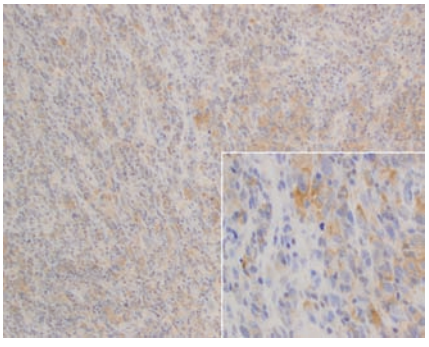

Figure 2. HSP90 paraffin section immunohistochemistry demonstrating 2+ cytoplasmic reactivity in interdigitating dendritic cell sarcoma cells. Higher magnification (40X) is displayed in lower right quadrant.

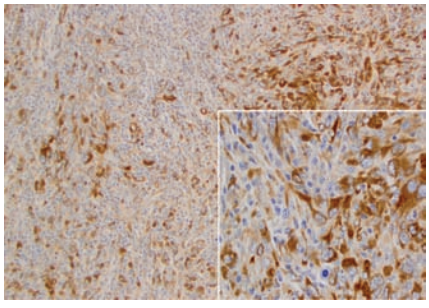

Figure 3. SPARC Polyclonal paraffin section immunohistochemistry demonstrating 3+ cytoplasmic reactivity in interdigitating dendritic cell sarcoma cells. Higher magnification (40X) is displayed in lower right quadrant.

extremely rare cancer with no approved systemic therapy. This tumor could not be classified into any of 39 tumor types on a CUP testing. Lastly, we attempted to characterize druggable targets using IHC profiling and found SPARC and HSP90 as potential targets with either commercially available or investigational agents under study. Molecular characterization of rare cancers may help enable investigators to identify a potential Achilles' heal that could improve the outcomes for patients with exceedingly uncommon malignancies.[8]

References

1. De Pas T, Spitaleri G, Pruneri G, et al. Dendritic cell sarcoma: an analytic overview of the literature and presentation of original five cases. Crit Rev Oncol Hematol 2008;65:1-7.
2. Von Hoff DD, Stephenson JJ, Rosen PJ, et al. A pilot study utilizing molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. AACR Abstract 2009, LB-259.
3. Gaertner EM, Tsokos M, Derringer GA, et al. Interdigitating Dendritic Cell Sarcoma A Report of Four Cases and Review of the Literature. Am J Clin Pathol 2001;115: 589-97.
4. Tai IT, Tang MJ. SPARC in cancer biology: its role in cancer progression and potential for therapy. Drug Resist Updat 2008;11: 231-46.
5. Raefsky E, Castillo R, Lahiry A, et al. Phase II study of neoadjuvant bevacizumab and trastuzumab administered with albumin-bound paclitaxel (nab paclitaxel) and carboplatin in HER2+ locally advanced breast cancer. J Clin Oncol 2008;26:abstr 627.
6. Von Hoff DD, Ramanathan R, Borad M, et al. SPARC correlation with response to gemcitabine (G) plus nab-paclitaxel (nab-P) in patients with advanced metastatic pancreatic cancer: A phase I/II study. J Clin Oncol 2009;27:abstr 4525.
7. Hahn JS. The Hsp90 chaperone machinery: from structure to drug development. BMB Rep 2009;42:623-30.
8. Stewart DJ, Kurzrock R. Cancer: the road to Amiens. J Clin Oncol 2009;27:328-33.