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CASE REPORT

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A Case Study of De-Staging and Reverse Transformation of a IDH Mutated Malignant Metastatic Sarcoma to Benign Tumor and Complete Clinical Remission by Application of Multi Targeted Epigenetic Therapies

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ABSTRACT

The evolution of spindle cell hemangiomas (SCH) to hemangiosarcomas is a phenomenon where although rare can occur. The fate of disease will certainly depend on its molecular behavior and as such clinical manifestation of the disease will depend on this transformation. Some articles have suggested that using traditional treatments such as radiation can influence this transition negatively. Reverse however has never been reported. In other words, there has been no report of angiosarcoma or for that matter any sarcomas transforming to a benign tumor. Here for the first we represent a case of a young woman with strong family history of sarcoma whose tumor responded to an epigenetic therapy with data suggesting a reverse transformation to a benign tumor. Further we believe larger studies should be conducted to evaluate this theory, as it can significantly change the way the treatments are designed for early stage disease in sarcoma.

ARTICLE HISTORY

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Background

The transformation of a benign hemangioma into a malignant angiosarcoma has been rarely reported, with only 11 cases reported in the literature. Maffucci syndrome is described in the literature with presentations of multiple enchondromas and hemangiomas, associated with an increased risk of developing malignant tumors [1]. These individuals harbor somatic mosaicism of mutations in isocitrate dehydrogenase 1 (IDH1) or isocitrate dehydrogenase 2 (IDH2), as the crucial factors in the pathogenesis of these diseases. The advances in detection of genetic alterations through liquid biopsy has enabled clinicians to not only detect the related alteration but also monitor the response to the therapy [2]. As such many times an actual tissue biopsy is not required, until excisional biopsy is performed through complete resection.

The role of IDH mutation has also been implied in GIST (SDH deficient), myelomas and gliomas.

Understanding spindle cell hemangiomas and their transformation to malignancy has evolved recently. Although treatment options that have been used for SCH include surgery, systemic steroids, cryotherapy, laser therapy, radiation therapy, cytotoxic drugs, selective embolization and recombinant interleukin-2 with varying degrees of success. The challenge however continues to exist for cases that metastasize or transform to malignant sarcomas. The local recurrence also is a challenge as it occurs more than 50 percent of the time [3].

The concept of switching on and off genes has been investigated for over two decades now, using epigenetic modifications. If we believe that a transformation form a benign lesion to a cancerous lesion could be controlled through the epigenome, the opposite could be quite possible. Results from studies using cell line model systems suggest that early critical epigenetic events occur in a stepwise fashion prior to cell immortalization. Epigenetic regulation resides at a nexus of gene–environment interactions. The process during which an immortal cell becomes malignant is completely influenced by epigenetic expressions, which include Htert/ P16,21 and Tp53 [4]. Further more using a combination of DNA demethylators and histone deacetylase inhibitors can reverse the epigenetic dysregulation and immortal cell transformation to malignant cells.

In the case of SCH transformation to chondrosarcoma, the target of interest could be defined based on presence of mutated allele frequency of altered gene, in the blood sample. Ideally if we can identify the altered gene, we can not only detect the best diagnostic prediction but also monitor response. In this case identification of IDH mutated gene in liquid biopsy was correlating with presence of spindle cells in the biopsy and nature of transformation to sarcoma. IDH alteration commonly is reported and in fact is differential for diagnosis of chondrosarcoma.

Somatic mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 occur in gliomas and acute myeloid leukaemia (AML)IDH1 and IDH2 mutations represent the first common genetic abnormalities to be identified in chondrosarcomas (about 80 percent), conventional central and periosteal cartilaginous tumours, and promoting chondrosarcoma growth through modulation of integrin, and in addition to inhibitors, CRISP technologies been developed to knockout the molecule [5-7].

IDH mutations have been reported to be involved in epigenetic remodeling ,stabilization of hypoxiainducible factor 1a (HIF1α),

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and regulation of alternative energetic pathways such as fatty acid metabolism. Mutant IDH1 and IDH2 chondrosarcomas display a 3.5-fold elevation of lactate, coupled with a trend for increase of pyruvate suggestive of enhanced glycolytic metabolism of glucose in mutant IDH chondrosarcomas [8].

The common metabolic pathway related to tumor growth in these tumors is glutamine. IDH1 in the cytosol plays a role as a source of NADPH for de novo lipogenesis and other biosynthetic pathways, whereas IDH2 participates both in oxidative flux of α-ketoglutarate to the later TCA cycle intermediates, as well as reductive carboxylation of α-ketoglutarate to isocitrate and citrate in the mitochondria.

Activation of reductive TCA cycle metabolism of glutamine and glutamate via conversion to αketoglutarate by the glutamate dehydrogenase reaction and flux to citrate via IDH2 has been invoked as a pathway for synthesis of biomass in growing cancer cells [9-10].

Case Study

On June 22,2022, a 24 years old female referred to us with a right ankle mass, 5 cm in size, which had been growing for over few months, and was ignored. The lesion was painful and uncomfortable.

In exam, there was a 5 cm round mass at lateral of right ankle, with firm presentation, and attached to surrounding tissue.

Initial labs confirmed the presence of CTC in her blood as well as circulating DNA manifesting the IDH2 altered gene. Since both her mother as well as her sister had cancer (lymphoma and melanoma respectively), and she had lost a sister at age 19 with osteosarcoma; she was assessed by a germline testing which identified SUFU 423A>G mutation.

Blood results had indicated increased Transforming growth factor (TGF - beta 1) at 18000, and her CTC was positive for c-Myc.

Chondrsarcomas manifest the IDH mutation about 50 percent of times, and the risk of recurrence is higher than usual, but these tumors are generally slow growing. There is relationship with CIMP phenotype and as such using epigenetic therapies are advised. HIF is also activated in these tumors, as such immediately she was started on IV epigenetic therapies consisting polyphenols that inhibit the DNA methyltrasferase. She received 20 IV treatments and her labs were repeated. Her TGF dropped down to 5304, on 8/26/22. Her cDNA completely disappeared post therapies. (See Figure 1)

Immunostain(s) performed on block A1:
SMA ..... Positive
S100 ..... Negative
HMB-45 ..... Negative

Immunostain(s) performed at NeoGenomics on block A1:
ERG..... Positive
HHV8 ..... Negative

(A0580398)
Patient MRN: N/A | DOB: MAR-25-1996 | Gender: Female
Diagnosis: Soft tissue sarcoma | Test Number 2

GUARDANT360
Therapy Finder Page

REPORTING		PHYSICIAN	
Report Date:	OCT-03-2022	Mohammad Nezami	
Receipt Date:	SEP-21-2022	Account: Orange Coast Medical Center of Hope	
Collection Date:	SEP-20-2022	Address: 496 Old Newport Blvd, Ste 7, Newport Beach, CA, 92663, United States	
Specimen:	Blood	Ph: 949 515-4673 | Fax: (949) 515-4672	
Status:	FINAL	Additional Recipient: N/A	

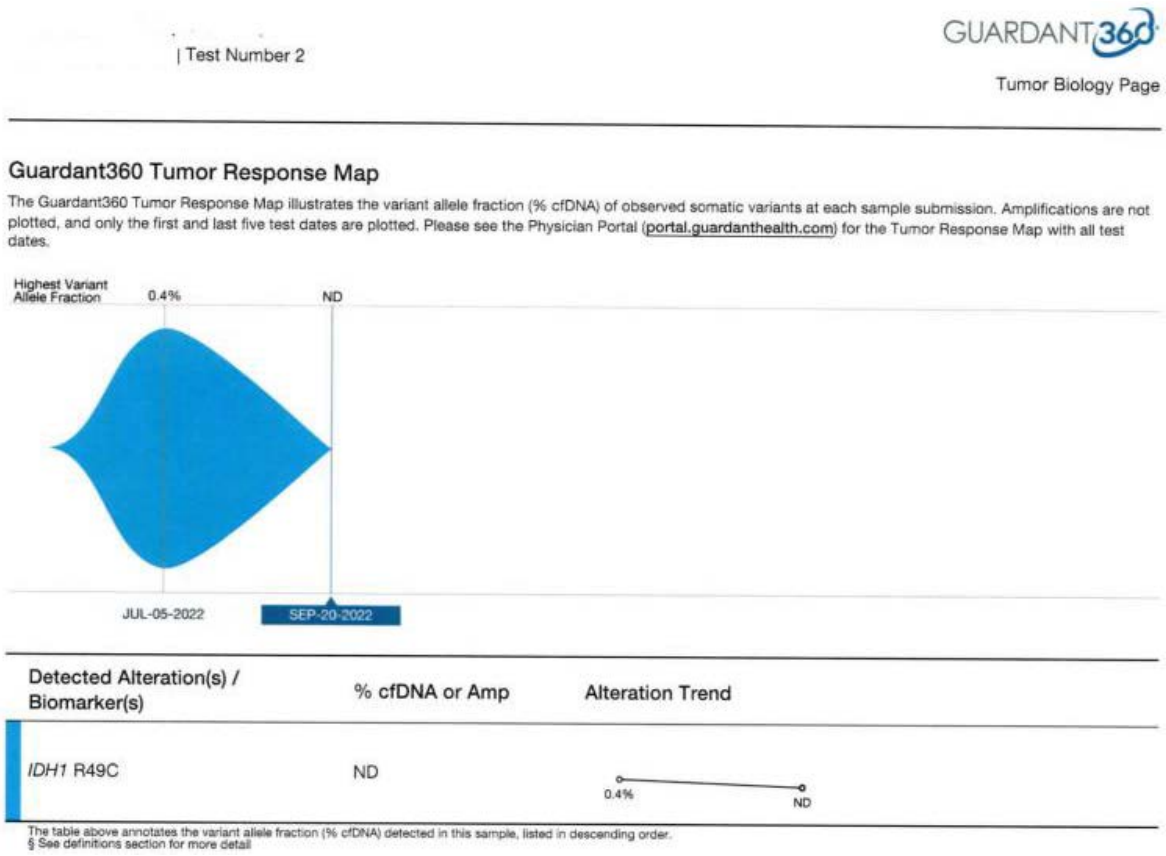
Complete Tumor Response Map on page 2

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability	% cfDNA or Amplification
No reportable tumor-related somatic alterations were detected in this patient's sample. This may be due to either absence of reportable mutations in the tumor itself or low levels of circulating tumor-derived cell-free DNA (ctDNA). Low ctDNA levels are most often encountered in patients with early stage or low volume disease, patients responding to therapy, and/or patients with stable disease. Clinical correlation is recommended with consideration for repeat Guardant360 testing of a new plasma or tissue sample when appropriate.			

Additional Biomarkers

Biomarker	Additional Details
Tumor Mutational Burden (TMB)	Not Evaluable
MSI-High	NOT DETECTED



| Test Number 2

GUARDANT360

Tumor Biology Page

Guardant360 Tumor Response Map

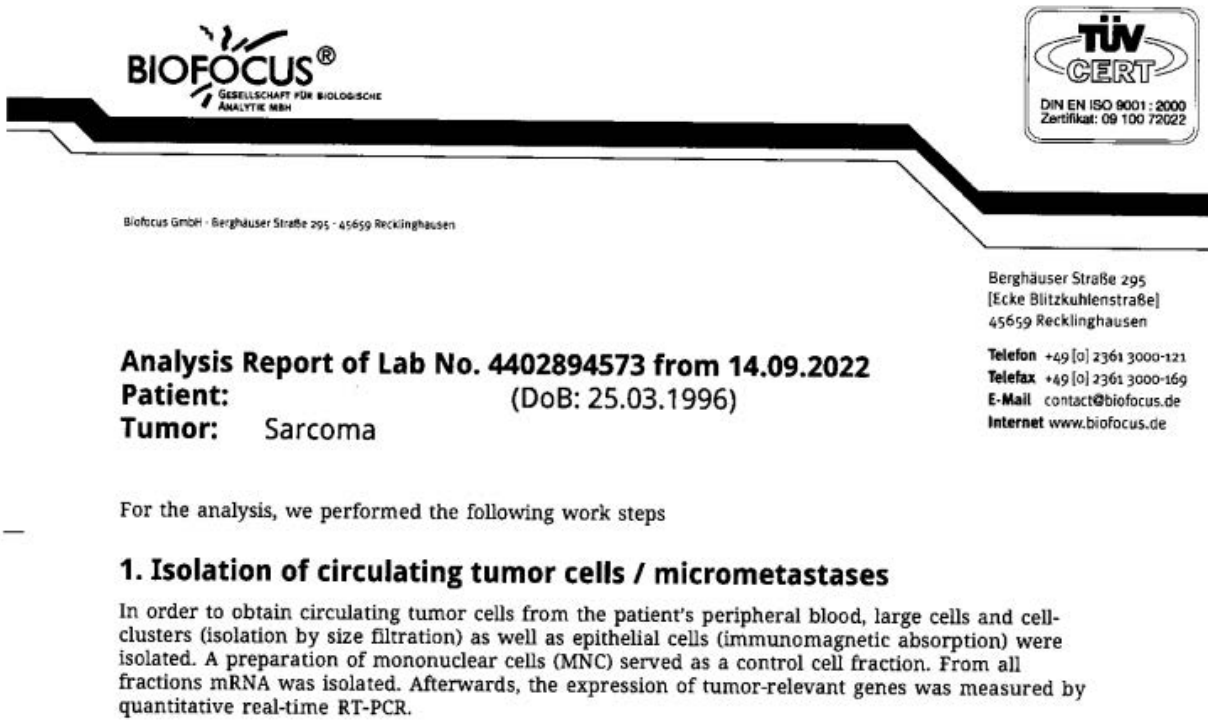
The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
IDH1 R49C	ND	0.4% → ND

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Figure 1: Circulating Tumor DNA (Pre and Post Therapy)

Her CTC completely resolved with the therapy. (Please see figure 2)



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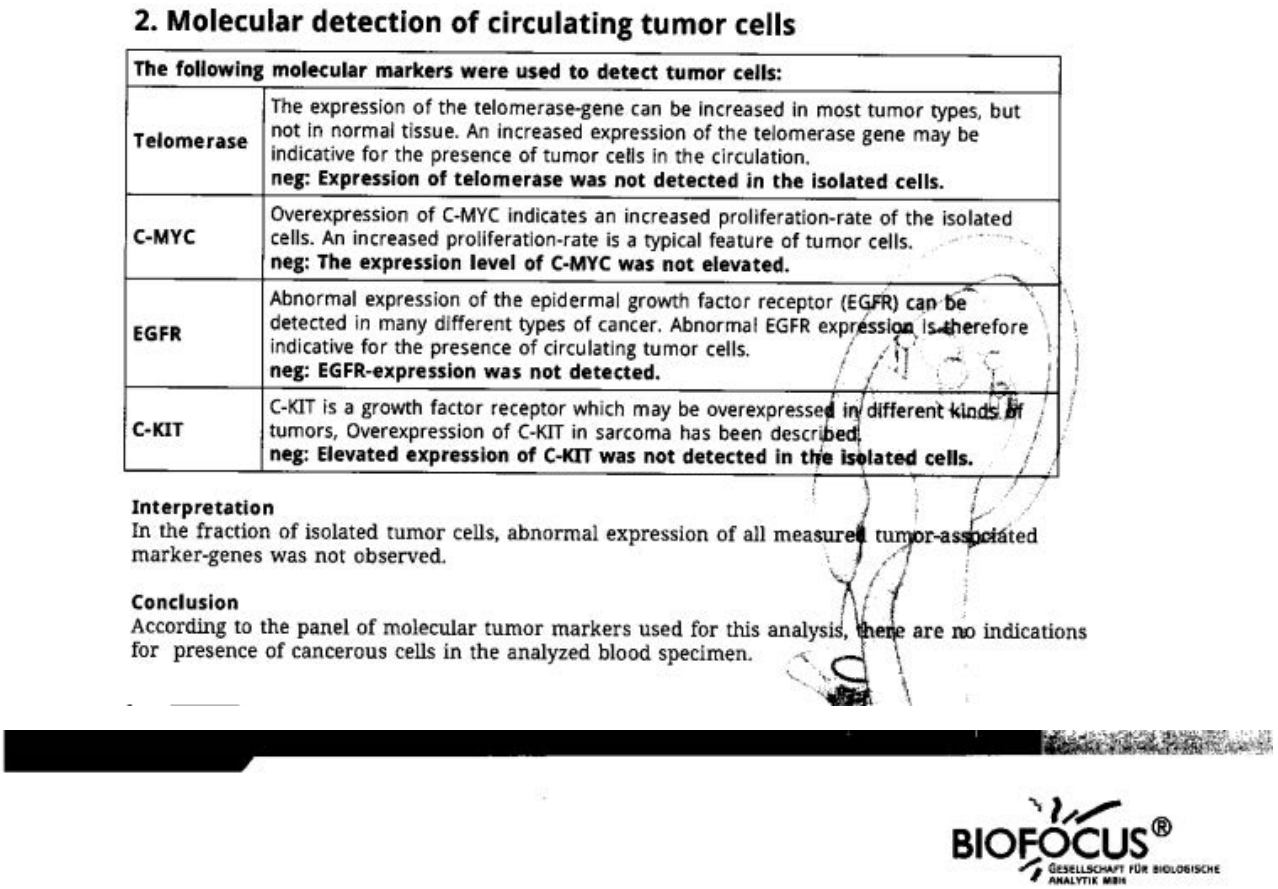
Analysis Report of Lab No. 4402894573 from 14.09.2022
Patient: (DoB: 25.03.1996)
Tumor: Sarcoma

For the analysis, we performed the following work steps

1. Isolation of circulating tumor cells / micrometastases

In order to obtain circulating tumor cells from the patient's peripheral blood, large cells and cell-clusters (isolation by size filtration) as well as epithelial cells (immunomagnetic absorption) were isolated. A preparation of mononuclear cells (MNC) served as a control cell fraction. From all fractions mRNA was isolated. Afterwards, the expression of tumor-relevant genes was measured by quantitative real-time RT-PCR.



2. Molecular detection of circulating tumor cells

The following molecular markers were used to detect tumor cells:	
Telomerase	The expression of the telomerase-gene can be increased in most tumor types, but not in normal tissue. An increased expression of the telomerase gene may be indicative for the presence of tumor cells in the circulation. **neg: Expression of telomerase was not detected in the isolated cells.**
C-MYC	Overexpression of C-MYC indicates an increased proliferation-rate of the isolated cells. An increased proliferation-rate is a typical feature of tumor cells. **neg: The expression level of C-MYC was not elevated.**
EGFR	Abnormal expression of the epidermal growth factor receptor (EGFR) can be detected in many different types of cancer. Abnormal EGFR expression is therefore indicative for the presence of circulating tumor cells. **neg: EGFR-expression was not detected.**
C-KIT	C-KIT is a growth factor receptor which may be overexpressed in different kinds of tumors, Overexpression of C-KIT in sarcoma has been described. **neg: Elevated expression of C-KIT was not detected in the isolated cells.**

Interpretation
In the fraction of isolated tumor cells, abnormal expression of all measured tumor-associated marker-genes was not observed.

Conclusion
According to the panel of molecular tumor markers used for this analysis, there are no indications for presence of cancerous cells in the analyzed blood specimen.

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3. comparison of present findings with former results

Compared to the former analysis from 7-Jul-2022, the expression level of the molecular tumor marker C-MYC has decreased and is below threshold. Markers EGFR, C-KIT and telomerase (TERT) are again in the normal range.

Date of analysis	Marker (threshold)			
	C-KIT (2.0)	C-MYC (2.0)	Telomerase (2.0)	EGFR (≥1 ceq)
14.09.2022	1,27	0,05	0	0
07.07.2022	0,84	**2,11**	0	0

*markers above threshold in **bold face**; ceq = cell equivalents

Conclusion:
The measured values of the detection markers suggest that the tumor cell burden in blood has decreased compared to the former analysis. There are no indications for presence of CTCs in the analyzed blood specimen.

Figure 2: Circulating Tumor Cell Analysis (CTC) Pre and Post Therapy

Further she underwent a resection by surgery on November, 15; 2022, and her mass was decreased to 1.6 X 1.4 cm. Her pathology showed no malignancy. There were only scant number of cells with SMA +, and as such the diagnosis was made as treated spindle cell hemangiosarcoma/ hemangiosarcoma. (ERG+)

She is currently in complete remission.

Discussion

Besides what we know about Maffucci syndrome which is historically described in the literature with presentations of multiple enchondromas and hemangiomas, associated with an increased risk of developing malignant tumors; our literature search did not manifest any recorded case of IDH positive/ mutated tumor which has been reported in the medical literature with transformations that involved a transitional state, specifically we did not find any reverse transition where the IDH mutated malignant tumor transformed into benign lesion by any treatment, including epigenetic therapies.

Our biological understanding of IDH role in epigenetic structure of tumor cells were also only limited to the unilateral role the IDH gene plays in genetic expression and metabolism of tumor cells. Here we were extremely encouraged to explore a completely different picture where it appears that the epigenetic regulation of IDH gene was in deed therapeutic, and beyond that we could draw the line on mechanistics of such therapy considering the role of TGF- Beta1, which was considered a target for this treatment. We already had known how modification of TGF-Beta1 is proved to impact epidermomesenchymal transition (EMT) and could explain why we were able to de-stage this disease (from micrometastatic stage four to localized tumor) and reflected in CTC response; but what we did not know was that such modification could in fact impact the gene expression at IDH. One explanation could be that TGF- Beta1 is also a hypermethylating factor and a possible mechanism could relate to it's inhibition by epigenetic therapies. Another possibility that could well explain the tumor shrinkage could be direct inhibition of glucose metabolism and hypoxia inducible factor 1 by multi targeted epigenetic therapies.

Conclusion

Our ability to translate a molecular process behind a clinical outcome is always limited by theories, but when an experiment is considered positive, evident by clinical outcome; one can rationalize the biological mechanisms, and generate further hypothesis. Here we, for the first time in oncology practice report a reversal of cancer to benign tumor, and de stage a disease simultaneously; using no cytotoxic therapy; which is by definition an expected process through epigenetic modifications.

Prevention in cancer is always classified into primary, secondary and tertiary. By this case, we conclude that prevention of cancer can well be still effective after a patient is in fact diagnosed. Such rationale could influence how we as clinicians approach the disease and further enhance our understanding on carcinogenesis and cancer prevention yet not classified. One could call this a new class of prevention where it falls between primary and secondary; as it consists of a reversal of disease.

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