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Case study

Metachronous cardiac and cerebral sarcomas: case report with focus on molecular findings and review of the literature☆

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Summary Although multiple primary malignancies are relatively rare, they have increased in frequency over the last decades, partly because of advances in diagnosis and therapy. This report describes for the first time the case of a patient with past occupational exposure to asbestos and no family history of cancer who developed 2 rare primary malignancies: a cardiac sarcoma and a gliosarcoma 11 months later. Molecular-cytogenetic studies did not identify common lesions to these 2 rare metachronous sarcomas. The gliosarcoma was associated with monosomy 10 and underlying *PTEN* monoallelic loss, which has been recurrently observed. In the cardiac sarcoma, *MDM2* amplification and *CDKN2AB*/9p21 biallelic deletion suggested intimal sarcoma. No causal relationship was found between cardiac sarcoma and asbestos exposure, although *MDM2* abnormalities were linked to malignant mesothelioma.

1. Introduction

Multiple primary malignancies (MPMs) are defined as the presence of 2 or more independent primary tumors [1], which may be synchronous if they are present at the same time or develop within 6 months of each other, or metachronous if the second malignancy develops at least 6 months after the first [2]. MPMs are due to genetic predisposition, immunodeficiency, exposure to carcinogens, or as a complication of chemotherapy or radiotherapy for the first tumor. The incidence of 2 different tumors at clinical and postmortem examination ranges from 3% to 5% [2], triple cancers occur in 0.5% of patients, and quadruple or quintuple cancers occur in less than 0.1% [3]. Here we report

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for the first time a metachronous combination of intimal sarcoma of the heart and gliosarcoma, illustrating the clinical, pathological, and genomic features and reviewing pertinent literature.

2. Case report

In April 2012, a 56-year-old man came to the Accident and Emergency Unit, Perugia General Hospital, because of the sudden onset of malaise, sweating, and restlessness. Case history showed professional exposure to asbestos for 9 years and 8 months, ending in 1993. A chest computed tomographic (CT) scan visualized a large (70 × 35 mm in size), hypodense mass with poor postcontrast enhancement. It filled most of the left atrium, passed through the mitral valve into the left ventricle, and extended to just below the aortic valve (Fig. 1A). Echocardiography confirmed the CT findings.

Because of cardiogenic shock, emergency cardiac surgery was performed. During extracorporeal circulation and cardioplegic arrest, the mass was excised from its base in the left atrial posterior wall. The postoperative course was uneventful, and the patient was discharged 9 days after surgery.

In May 2012, the patient started chemotherapy: 8 cycles of epirubicine (30 mg/mq day, 1-2 every 21 days) and ifosfamide (1000 mg/mq day, 1-3 every 21 days). In October 2012, positron emission tomography CT showed a complete response. In February 2013, the patient developed dysarthria, dysgraphia, and lateral right homonymous hemianopsia. Brain-contrast magnetic resonance imaging showed a lesion about 70 mm in diameter in the left frontotemporal lobe (Fig. 2A). A positron emission tomography CT scan excluded distant metastasis and local recurrence of the atrial lesion. In March 2013, the tumor mass was removed via temporal craniotomy. The first dose of chemoradiotherapy was administered intraoperatively, and treatment continued postoperatively until June 2013. A check-up in July detected G1 thrombocytopenia according to Radiation Therapy Oncology Group (RTOG), ataxia, and right limb weakness. In August 2013, the patient died after a short coma. A postmortem examination was not performed.

3. Materials and methods

3.1. Histopathology and immunohistochemistry

All surgical specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using the commercial antibodies listed in the Table. MDM2 immunolabelling was also performed to classify the cardiac lesion better [4]. A biotin-free polymeric horseradish peroxidase linker antibody conjugate system (Bond Polymer Define Detection; Vision Biosystems Ltd, Mount Waverly, Victoria, Australia) was used on the Leica Bond III automated immunostainer (Vision Biosystems Ltd).

3.2. Cytogenetic studies

Fluorescent in situ hybridization (FISH) was performed on 4-μm sections of both tumors as previously described [5]. Briefly, after pretreatment to remove paraffin, slides were treated with hydrochloric acid (HCl) 0.2 N and sodium thiocyanate (NaSCN), fixed in formalin solution, and dehydrated in ethanols (70%/85%/100%). Probes for *PDGFRA*/4q12 (RP11-3H20, RP11-24O10), *EGFR*/7p12, *EWSR1*/22q21, *DDIT3*/12q13.1-q13.2, and *CDKN2A*/9p21-CEP9 (Vysis-Abbott, Milan, Italy) were used to investigate both tumors. On chromosome 12, probe for *DDIT3* (position 57910371-57914300, UCSC GRCh37) encompassed *CDK4* (position 58141510-58146230). Rearrangements of *MDM2*/12q15, *FOXO1*/13q14, *FUS*/16p11.2, *SYT*/18q11.2 (Vysis-Abbott, Abbott Park, IL), and *TFE3*/Xp11.22 (Kreatech Diagnostic, Resnova, Genzano, Italy) were investigated in the cardiac mass, and rearrangements of *PDGFRB*/5q33 (RP11-759G10, RP11-100O5), *RB1*/13q14 (RP11-174I10, RP11-305D15), 1p36/1q25 and 19q13/19p13, *PTEN*/10q23, and *TP53*/17p13.1 (Vysis-Abbott) were sought in the cerebral mass. An orange- labeled probe L1.84 [6] evaluated chromosome 18 numerical abnormalities. All probes were tested and validated on peripheral blood T lymphocytes obtained from healthy donors to exclude nonspecific binding. At least 150 intact nonoverlapping cells were analyzed for each experiment by fluorescence microscope Olympus BX61 (Olympus, Milan, Italy) equipped with a highly sensitive camera JAI (Copenhagen, Denmark) and driven by CytoVision 4.5.4 software (Genetix, New Milton, Hampshire, UK).

4. Results

4.1. Gross, histopathologic, and cytogenetic findings of cardiac mass

The cardiac lesion was hard, 70 mm in diameter, and yellow-grayish, and had hemorrhagic areas. Microscopically, it was highly cellular and vascularized. Monomorphic spindle cells with high mitotic index were observed together with coagulative necrosis lined by “palisading” tumor cells (Fig. 1B and C). Immunohistochemistry showed widespread CD99 positivity (Fig. 1D), plurifocal reactivity for Bcl2 (Fig. 1E) and CD34 (Fig. 1F), and focal vimentin positivity. Neoplastic cells were negative for calretinin, CD31, factor VIII–related antigen, S-100, smooth muscle actin, desmin, caldesmon, epithelial membrane antigen (EMA), cytokeratin AE1/AE3, and MDM2 (Table). Although morphology and CD99 positivity suggested monophasic synovial sarcoma, FISH analysis did not detect the pathognomonic translocation t(X,18)(p11.2;q11.2). *DDIT3*, *FKHR1*, and *FUS* probes showed 20% to 30% of cells had 3 signals, indicating trisomy of chromosomes 12, 13, and 16. The probe for *SYT* gave 3 signals in about 20% of cells, 4 signals in 30%, and 5-n signals in 30%. Chromosome 18 polysomy was confirmed by