

Efficacy of First Line Doxorubicin and Ifosfamide in Primary Cardiac Synovial Sarcoma

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Synovial sarcomas are rare entities accounting for less than 1% in all primary cardiac tumors. These tumors are extremely aggressive and generally have a poor prognosis. We report a recent case from Agripa Ionescu Emergency Clinical Hospital Bucharest. A 33-years-old Caucasian male was diagnosed in April 2013 with right ventricle tumor. Histopathological examination indicated a biphasic synovial sarcoma (G3). Both intra-cardiac ventricle tumor and tricuspid valve were removed through surgical atrium-ventricle double approach and tricuspid valve was replaced with biological prosthesis. Post-surgery evolution was favorable, thoracic and abdominal CT scans didn't give evidence of metastasis. The patient received adjuvant chemotherapy with doxorubicin and ifosfamide and was free of disease on regular follow-ups for 16 months.

Keywords: cardiac synovial sarcoma, treatment, survival, adjuvant chemotherapy

Synovial sarcomas are malignant soft-tissue tumors that manifest both in joint cavities and other sites that are devoid of synovium (head, neck, lung, heart and abdomen) [2]. In spite of histological images resembling with synovium with epithelioid differentiation, this tumor is not considered to be originated from synovial tissue [10, 12].

Primary heart tumors are rare, with a prevalence of only 0.001-0.003%, most of the cardiac tumors being metastatic lesions. Although the true incidence has probably been underestimated, synovial sarcomas account for approximately 5% of cardiac sarcomas [12]. That is why cardiac primary synovial sarcoma is mentioned in the literature mainly as case reports. According to IARC, an association between cardiac synovial sarcoma and asbestos exposure has been reported [7]. Synovial sarcoma is a monophasic or a biphasic tumor composed of spindled and epithelioid areas, characterized by reciprocal translocation SYT-SST: t(X;18)(p11.2;q11.2) which is seen in more than 90% of soft tissue synovial sarcomas [7].

The clinical manifestations of the disease are non specific and are related with obstruction of the flow within the heart: dyspnea, chest pain, cough, fatigue, syncope, vomiting and embolism [9, 10, 13]. Opposite to soft tissue synovial sarcoma, for cardiac synovial sarcoma there is a clear-cut male predominance and a mean age of 32.5 years. These tumors are extremely aggressive with survival rates less than 1 year, and require multidisciplinary approaches including surgery, chemotherapy, and radiotherapy [9, 10, 13].

Management of malignant cardiac tumors has always been a challenge for cardiac surgeons, due to invasive growth and limitations of resection inside the heart. Complete resection is seldom possible. In most of the cases, the histopathological diagnosis can be provided after surgery.

Experimental part

Here we report our experience with a recent case from Agripa Ionescu Emergency Clinical Hospital Bucharest. The patient aged 33, male, without known previous cardiac disease was diagnosed in April 2013 with right ventricle tumor (fig. 1). The patient was overweight, with chief complaints of significant bilateral leg edemas for 2 months, without other symptoms, with good general condition, hemodynamically and respiratory stable. Both the laboratory findings and rest ECG were within normal parameters.

Surgery was carried out under total hemodilution, moderate hypothermia and cold cardioplegia and showed a massive tumor originated in the free wall of the right ventricle that involved also the tricuspid valve. By atrium-ventricle double approach, the intra-cardiac ventricle tumor together with tricuspid valve was removed and replacement of tricuspid valve with biological prosthesis was also performed.

Histopathological examination indicated a biphasic synovial sarcoma (G3). The immunohistochemical staining showed that EMA was diffusely positive in the glandular component; CK7 and calretinin were focally positive in epithelial cells; CD 99, CD34, S100 were negative; fusiform cells showed positive reactions to vimentin and Bcl. 20% percent of tumor cells were staining positive for proliferation marker Ki-67. Post-surgery evolution was favorable, without complications. Following treatment for high blood pressure (Tertensif - 1.5mg at 2 days, Metoprolol 25mg twice per day) and anticoagulant treatment (Sintrom - 4 mg, daily), the patient was hemodynamically and respiratory stable. The evaluation of recurrence based on thoracic and abdominal CT scans (May 2013) revealed no liver or lung metastasis, but showed 12 mm paratracheal lymphadenopathy.

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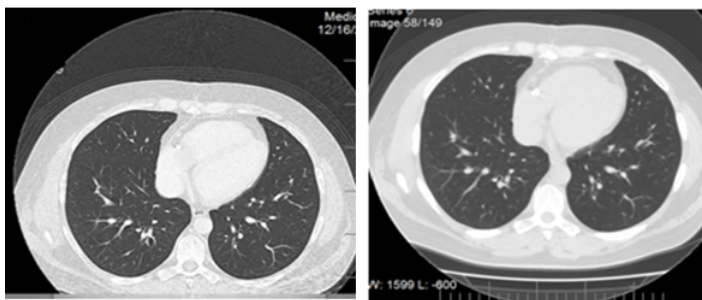


Fig. 1. CT scan: right ventricle tumor

Adjuvant chemotherapy followed BBCA administration guidelines and consisted of doxorubicin 50 mg/m² IV push, Mesna 600 mg/m² IV in 100 mL D5W (dextrose 5 % in water) over 15 min, ifosfamide 5000 mg/m² IV in 3000mL of D5NS (dextrose 5% in normal saline) with Mesna 2500 mg/m² to infuse over 24 h and Mesna 1250 mg/m² IV in 2000mL of D5NS to infuse over 12 h, repeated every 21 days [4]. Furthermore, G-CSF was indicated for the secondary prophylaxis of neutropenia.

Treatment toxicity was evaluated based on National Cancer Institute criteria. Chemotherapy was well tolerated and only grade 1 hematological toxicity (leukopenia—without thrombocytopenia) was found [11].

Following the end of chemotherapy (December 2013), a thoracic CT scan indicated lymph nodes measuring 6.3 and 9 mm under carina, and lymph nodes up to 5 mm in diameter (with some areas of hypocaptation) in Baretz's space. As compared to the CT scan from May 2013, the lymphadenopathy regressed. There was no identification of any metastatic tumor in the lungs or liver. The echocardiography detected no hyperechoic masses.

The PET-CT scan performed in May 2014 noted no metabolic active images in mediastinal, supra- and sub-diaphragmatic lymph nodes but displayed moderate uptake of FDG (2-fluoro-2-deoxy-D-glucose) in sternum (fig. 2). Bones, lungs, liver and pancreas exhibited normal aspect, without any active metabolic lesions. Renal excretion was within physiological parameters and intestinal FDG uptake was normal.

To date, the patient was alive and free of disease 16 months from diagnosis, without any local or distance recurrence signs.

Results and discussions

Primary cardiac synovial sarcoma was first described in 1978 and is an exceedingly rare type of tumor [1]. According to the literature data, tumors locate predominantly to the right side of the heart, as it is the case with our patient [6, 7, 10]. Still, left-sided lesions exhibit a smaller size as compare to right-sided lesions due to earlier onset of the space-occupying related symptoms [7, 10]. Especially with tumors located in unusual regions, diagnosis can be challenging. Besides the clinical exam, trans-thoracic/transoesophageal echocardiogram represents the first line of investigations.

ECG, Chest X-ray, CT scan or MRI scan are usually performed in most of the cases. Transvenous endomyocardial biopsy may also be helpful to confirm the diagnosis prior to operation [3].

The hallmark of the diagnosis is represented by immunohistochemistry and molecular genetic studies [6, 7]. The differential diagnostic should be done with malignant peripheral nerve sheath tumor, carcinoma and diffuse type tenosynovial giant cell tumor [12]. As compared to malignant peripheral nerve sheath tumor, biphasic synovial sarcoma rarely involves nerves and exhibits frequent calcification and hemangio-

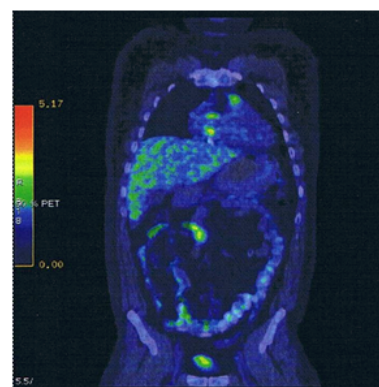
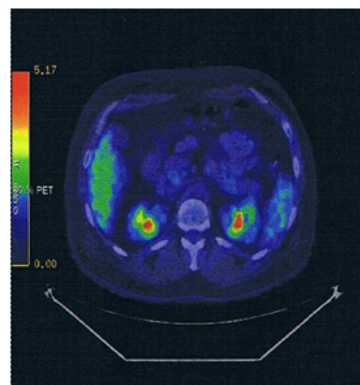
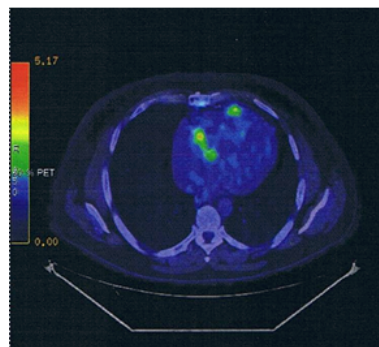
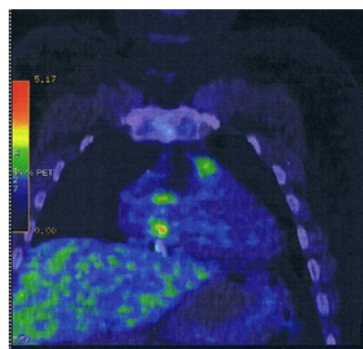


Fig. 2. Images of PET-CT scan (May 2014)

pericytomatous vessels. Opposite to carcinoma, biphasic synovial sarcoma presents SYT-SST gene fusion and high TLE1 expression. The difference between biphasic synovial sarcoma and diffuse type tenosynovial giant cell tumor consists of positive staining for keratin and localization (very rarely involves joints). The laboratory test appear to be nonspecific for the diagnosis [8].

The main treatment is represented by surgery even though complete removal of the tumor is questionable in some cases. Autotransplantation after the resection of the tumor have been used in few cases [10]. The type of operation with highest rates of success is sternotomy and cardiopulmonary bypass [8]. Adjuvant chemoradiation is considered valuable but survival time seldom exceeds 12 months due to local recurrences [6]. Patients with complete removal of the tumor, younger age, without

complex chromosomal abnormalities and tumor originated from the pericardium are considered to have a better prognosis [7, 10].

As compared to other soft tissue sarcomas, synovial sarcoma is relatively sensitive to ifosfamide and doxorubicin but the results are still not satisfactory [5]. In spite of high toxicity (neutropenia, anemia, leukopenia, nausea, vomiting, alopecia, hematuria etc), there is no other standard therapy that is clearly superior [1, 8]. Mesna is a synthetic sulfhydryl (thiol) compound that is usually co-administrated ifosfamide in order to reduce its harmful effect in bladder and kidney.

However, synovial sarcoma represents a suitable aspirant for molecular targeting and a phase I study using STT/SST derived junction peptide vaccine has proved some efficacy [1, 8].

Conclusions

We have reported a patient with primary cardiac synovial sarcoma presenting in the right ventricle. The patient underwent surgery and received adjuvant chemotherapy with doxorubicin and ifosfamide and was free of disease on regular follow-ups for 16 months. Cardiac sarcomas are extremely rare and have a poor prognosis; occasional long-term survival can be obtained with aggressive therapy (combining chemotherapy with surgical resection of metastases) in situations where the disease is limited. In future, targeted therapy with new agents is believed to alleviate significantly the outcome.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References

1. BOULMAY B, COOPER G, REITH JD, MARSH R. Primary cardiac synovial sarcoma: a case report and brief review of the literature. *Sarcoma*. 2007;2007:94797.

2. HUO Z, LU H, MAO Q, JIN Z, WU H, FENG X, XIAO Y, WANG Y, GUO L. Primary synovial sarcoma of the right heart involving the tricuspid valve in an elderly Chinese woman: a case report. *Diagn Pathol*. 2015;10:80.

3. HUSSAIN S, KHAN AA, KHAN Q. Synovial sarcoma of the heart. *J Coll Physicians Surg Pak*. 2012;22(11):723-5.

4. TRAVIS W.D., BRAMBILLA E., MULLER-HERMELINK H.K., HARRIS C.C. (Eds.): *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. IARC Press: Lyon 2004

5. JUDSON, I., VERWEIJ, J., GELDERBLOM, H., HARTMANN, J.T., SCHÖFFSKI, P., BLAY, J.Y., European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-23.

6. TALUKDER, M., JOYCE, L., MARKS, R., KAPLAN, K., Primary cardiac synovial sarcoma. *Interact Cardiovasc Thorac Surg*. 2010;11(4):490-2.

7. VARMA, T., ADEGBOYEGA, P., Primary cardiac synovial sarcoma. *Arch Pathol Lab Med*. 2012;136(4):454-8.

8. WANG, J.G., LI, N.N., Primary cardiac synovial sarcoma. *Ann Thorac Surg*. 2013;95(6):2202-9.

9. YOKOUCHI, Y., HIRUTA, N., OHARASEKI, T., IHARA, F., ODA, Y., ITO, S., YAMASHITA, H., OZAKI, S., GOMI, T., TAKAHASHI, K., Primary cardiac synovial sarcoma: a case report and literature review. *Pathol Int*. 2011;61(3):150-5.

10. ZHANG, L., QIAN, J., LI, Z., JING, H., Primary synovial sarcoma of the heart. *Cardiol J*. 2011;18(2):128-33.

11. ***http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf

12. *** http://surgpatheria.stanford.edu/softmisc/synovial_sarcoma/differentialdiagnosis.html

13. *** http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Sarcoma/SAAI_Protocol_1Mar2013.pdf

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