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Sudden Death of a Young Adult during Chemotherapy for Testicular Carcinoma; Role of Forensic Pathologist in Evaluating the Treatment Outcome and Medical Negligence

A Case Report with Literature Review

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Abstract:- Testicular germ-cell carcinoma (TGCC) is curable. Three-drug combination chemotherapy for testicular tumors (BEP therapy: bleomycin, etoposide, and cisplatin) is performed as standard treatment following orchiectomy. A 21- year- old male had a hard painless left testicular lump for two months. Investigations revealed elevated levels of serum beta-HCG and alpha-fetoprotein. Testicular tumor with left para aortic lymph node involvement was diagnosed after a CT scan. Left inguinal radical orchiectomy was performed and histology revealed that mixed germ cell tumor composed predominantly of yolk sac carcinoma (50%) associated with seminoma (30%) and embryonic carcinoma (20%). The oncologist decided to treat him with four cycles of chemotherapy with BEP regime. He was given the first chemotherapy. However, he was found collapsed before completion of the second cycle of chemotherapy in the ward bath room. Autopsy revealed that total alopecia, hypo pigmented healed marks of chickenpox and left inguinal scar with absence of the testis. Serial dissection of left common trunk and anterior descending branch of coronary arteries revealed a thrombus completely occluding the lumen. Yellowish necrotic area with intermittent fresh hemorrhages were found in the anterior and postero-lateral walls of left ventricle. There were no risk factors or family history for premature coronary events. End of the autopsy, the cause of death was given as acute myocardial infarction due to coronary thrombus in a subject with chemotherapy for testicular carcinoma. This case strengthens the previous studies of induction of Virchow's triad and early formation of thrombus with myocardial events during the chemotherapy for testicular carcinoma. This case report reiterates the importance of cardiac assessment prior to chemotherapy to avoid unnecessary litigation cases.

Keywords:- *Chemotherapy, BEP, Myocardial Infarction, Testicular Cancer, Thromboembolism, Medical Negligence, Forensic Pathologist.*

I. INTRODUCTION

Dying of young patient when under the care of clinician for chemotherapy is not only distressing event to family members but also clinician too. When patient dies under chemotherapy for curable cancer due to unexpected events cause frustration among family members and allegation of medical negligent against clinicians. It may be a difficult task to Forensic Pathologist to confirm or exclude the chain of events led to death following chemotherapy without excluding other possible causes of death. Here we report a young patient with testicular tumor who developed acute myocardial infarction (AMI) during combination of chemotherapy in the ward with significant medical negligence allegations by relatives.

II. CASE REPORT

A 21-year-old male presented with a hard painless left testicular lump of two months duration. Investigations revealed elevated levels of serum beta-HCG and alpha-fetoprotein. A testicular tumour with left para aortic lymph node involvement was diagnosed on a CT scan. Left inguinal radical orchiectomy was performed and histopathology revealed that mixed germ cell tumour composed predominantly of yolk sac tumour (50%) associated with a seminoma (30%) and an embryonic carcinoma (20%).

Four cycles of chemotherapy with bleomycin, etoposide, and cisplatin (BEP) regime was initiated, but he was found collapsed in the ward bathroom before a day of completion of the second cycle of chemotherapy.

Autopsy revealed total alopecia (figure 01), hypo-pigmented healed marks of chickenpox (figure 01) and a left inguinal scar with presence of only the right testis (Figure 02). Serial dissection of left common trunk and anterior descending branch of coronary arteries showed a thrombus completely occluding the lumen (figure 03). Yellowish necrotic areas with intermittent fresh hemorrhages were found in the anterior and postero-lateral walls of left ventricle (figure04, 05, 06). Histopathological studies of

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coronary artery revealed that fresh and organizing thrombus with varying ages. Area of myocardium revealed that loss of nuclei of myocytes, fragmentation of cell walls, necrosis of myocytes and predominant macrophages and number of neutrophils. RBCs were detected between the intact and necrotic myocytes. Lungs, brain and bowel did not show evidence of thrombo embolic events. Histology of the lung did not show changes of pneumonia or acute respiratory distress syndrome. (ARDS)

There were no risk factors or a family history for premature coronary events and hyper coagulable state suggestive of Protein C, S and Antithrombin 3 deficiencies, factor v Leiden mutation and etc. The cause of death was given as an acute myocardial infarction due to a coronary thrombus in a subject undergoing chemotherapy for a testicular carcinoma at the end of the autopsy. Relatives of the deceased alleged against clinician to fail to detect this coronary events even though patients was undergoing chemotherapy in the ward for six days.

Figure 01

Figure 02

Total alopecia (figure 01), hypo-pigmented healed marks of chickenpox (figure 01) and a left inguinal scar with presence of only the right testis (Figure 02).

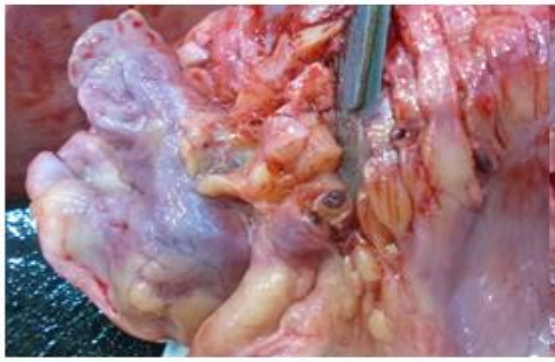

Figure 03

Figure 04

Thrombus completely occluding the lumen (figure 03) and fresh infarcted area of myocardium (figure04)

Figure 05

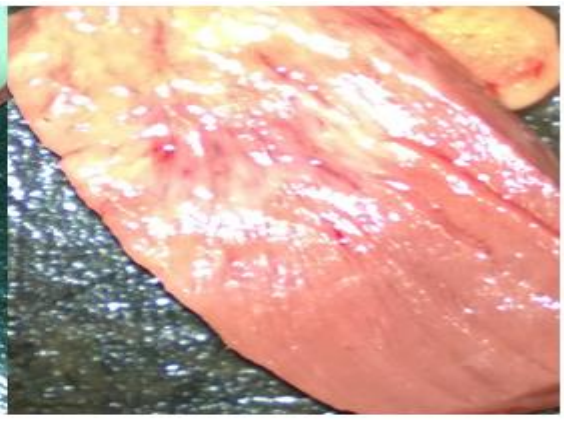

Figure 06

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Yellowish necrotic areas with intermittent fresh hemorrhages were found in the anterior and postero-lateral walls of left ventricle (figure 05 and 06)

III. DISCUSSION

Testicular germ-cell malignancy (TGCC) is an example of a curable cancer[01] and most common cancer in 25 to 35 year old men commonly known in two main categories, seminomas and non-seminomas .The exact causes for testicular cancer is not known but risk factors include undescended testicles, congenital abnormalities, cancer history of testicular cancer in one testis ,family history of cancer, HIV infection and being white[02]Five year survival rate is very good in localized tumor [99%] and retro peritoneal lymph node involvement [96%] and beyond the retroperitoneal lymph node involvement [73%] fallowing surgery and chemo radiotherapy [03] Radical orchidectomy is main stay of surgical treatment. After an orchidectomy, standard treatment of disseminated non-seminoma consists of chemotherapy with a combination of bleomycin, etoposide, and cisplatin. Approximately 80% of patients with a disseminated non seminoma then become long-term survivors [04)

The development of thrombotic complications during cancer treatment may result from tumor-associated hyper coagulability, compression of blood vessels by tumor, direct damage from venous access ports, and possibly chemotherapy induced endothelial damage [05]

Thrombotic complications might predispose major cardiovascular events such as MI, strokes and arterio venous thrombo embolism in other vessels. This case is one of the examples of myocardial infarction due coronary thrombosis. In this case, origin of thrombus is most likely to be due to chemo therapy fallowing testicular germ cell tumor, because victim was 23-year-old and did not have other risk factors for premature vascular event such as family history, obesity (BMI), hypertension, diabetes, smoking and etc. (Trauma)

These observations in conjunction with previous reports [06] indicate that MIs occurring in chemotherapy in young patients are commonly caused by thromboembolic events rather than by atherosclerotic stenosis. Cerebral strokes, bowel infarction, pulmonary thrombo embolism and peripheral arterial occlusions are probably induced by the same mechanism. Vasospasms secondary to chemotherapy could be another mechanism [07]

Most of the literature suggest that mechanisms for hyper coagulable state are due to thrombogenic property of tumor by activating the thrombin directly and chemotherapy induced endothelial damage releasing increased amount of vWF and chemotherapy induced inflammation and inflammatory mediators activating the coagulation cascade indirectly. This case supports the facts of induction of hypercoagulable state [Virchow's triad] fallowing chemotherapy for testicular cancer.

An association between vWF and arterial thrombosis in cisplatin-treated patients was studied by Licciardello et al. Pulmonary fibrosis can be induced by Long-term therapy with bleomycin, which upsurges interleukin-1 manufacture in alveolar macrophages. As a mechanism, interleukin-1 produced in the lung may act on the vascular endothelium of the whole body, promoting coagulation [08]. This lung fibrosis is not detected in our case.

An increased intima – media thickness of the carotid artery is associated with a higher prevalence of vascular risk factors and with an increased risk of myocardial infarction and stroke [09, 10, and 11]. Even though no thrombus was detected in carotid artery and which were normal in appearance accurate measurement of intima – media thickness was not done in this case.

A nationwide survey was conducted in Germany during 2006–2008, to ascertain cardio vascular events occurring in testicular germ cell tumour(TGCC)patients during chemotherapy or within 6 weeks of chemotherapy revealed that common place of thrombus was with in left anterior descending artery [12]. It was consistence with our case study and in our case victim was died during second cycle of chemotherapy and before a day of completion.

Other possible causes of sudden death in this case were tumor lysis syndrome and acute pulmonary thrombo embolism due to deep vein thrombosis following chemotherapy. Group of metabolic turbulences that arises when large numbers of neoplastic cells are destroyed quickly, leading to the discharge of intracellular ions and metabolic byproducts into the systemic flow. This is characterized by rapid expansion of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute kidney damage [13, 14]. It occurs commonly after the start of initial chemotherapeutic treatment, but unplanned cases have more and more been documented in patients with high-grade hematologic malignancies [15]. Available ante mortem reports revealed normal electrolytes, serum calcium and blood urea and exclude tumor lysis syndrome and autopsy did not reveal that pulmonary thrombo embolism.

Available ante mortem reports did not reveal any cardiac assessment or clotting profile including PT/INR which was done during and after the chemotherapy.

Patient was very young, well and did not reveal history of chest pain or breathing difficulties except tiredness while was in the ward or at home during/after the chemotherapy. So above assessment may not be indicated clinically.

This case report suggests that this death might be preventable if clinician did the cardiac assessment and anti-thrombotic treatment as soon as earlier before or after the development of coronary thrombosis. [16] According to the literature deaths due to thrombotic events were reported when chemotherapy given in ambulatory outpatients division. [17] It is rarely reported when patient was in inward chemotherapy. Previous small numbers of literatures also support same fact as mentioned above even though

these are rare complications of treatment at least in high risk patient. This fact should be studied further by relevant professionals in future to prevent mortality and morbidity related to chemotherapy. Allegation of medical negligent against clinician will be decided in the civil court in future trial with the help of other specialist. Because prognosis of the patient in thrombotic events is poor when compared with other control. [18] There may be part of the negligent because of the failure of the clinician in detecting thrombotic events and lack of initiation of early fibrinolytic therapy. Forensic Pathologist can play role not only to resolve medical negligent issues, but also can help clinician to evaluate the treatment outcome as highlighted in this case.

IV. CONCLUSIONS

This case highlighted that significant role of Forensic Pathologist not only in resolving medico-legal issues related to treatment, but also in evaluating treatment outcome by doing gold standard autopsy. This case also strengthens the previous studies that of administration of chemotherapy initiates thrombus formation with associated myocardial events during chemotherapy for testicular carcinoma. This case report reiterates the importance of cardiac assessment prior to chemotherapy and prophylactic anticoagulant treatment at least in vulnerable patients to avoid medico-legal litigation. The fact should be studied further by relevant professionals in future to prevent mortality and morbidity related to chemotherapy to increase the awareness among clinicians.

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