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Marfan syndrome and multiple myeloma: A coincidence or tendency?

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Abstract

Introduction: Marfan Syndrome (MFS) is an autosomal dominant connective tissue disorder characterized by musculoskeletal, ocular, and cardiovascular abnormalities. It results from a mutation in the fibrillin-1 gene, leading to its deficiency and often causing overactivation of the TGF-β signaling pathway, which may contribute to cancer development. Numerous case reports and a case-control study have noted the coexistence of MFS with solid and hematologic malignancies.

Case report: We present a 60-year-old male diagnosed with Multiple Myeloma (MM) after genetic tests revealed MFS due to a barrel chest deformity. He experienced back pain and fatigue for ten months and had a history of hypertension and hyperthyroidism. Physical examination revealed tall stature and barrel chest. Laboratory tests indicated anemia and monoclonal gammopathy, while PET/CT identified lytic lesions in the vertebrae. Genetic analysis confirmed an FBN1 mutation.

Conclusion: Fibrillins are crucial for the extracellular matrix and may influence malignant processes. The TGF-β pathway, often disrupted in tumors, plays a role in MM pathogenesis. This report highlights the potential link between MFS and MM, marking the first documented case of their coexistence.

Keywords: Marfan syndrome; Myeloma multiple; Transforming growth factors.

Introduction

Marfan Syndrome (MFS) is an autosomal dominant genetic disorder of connective tissue characterized by musculoskeletal, ocular, and cardiovascular abnormalities [1]. MFS involves a mutation of the gene for the extracellular matrix protein fibrillin-1, resulting in its deficiency; this is often accompanied by overactivation of the transforming growth factor-β (TGF-β) signaling pathway, which may have a role in cancer pathogenesis [2]. Many published anecdotal case reports and a case-control study have described the coexistence of Marfan syndrome and solid and hematologic malignancies [2]. We present a patient who was diagnosed with multiple myeloma and was diagnosed with MFS as a result of genetic tests prompted by a barrel chest finding on physical examination.

Case presentation

A sixty-year-old male patient was admitted due to backache and fatigue of ten months' duration. He had a history of essential hypertension and hyperthyroidism. Physical examination showed a tall stature (190 cm) and a barrel chest deformity (Figure 1).

Family history disclosed that a sister was similar in height and had a history of heart valve surgery. Her daughter also had a barrel chest deformity, as shown by physical examination. The patient's laboratory tests showed anemia (Hb: 7.9 g/dL), high sedimentation rate (96 mm/h), albumin/globulin inversion, and Rouleaux formation in his peripheral blood smear. Serum immunofixation electrophoresis was consistent with IgA ʎ monoclonal gammopathy, and bone marrow biopsy demonstrated 80% plasma cell infiltration. PET/CT detected hypometabolic lytic lesions in T2, T8, and T9 vertebrae. The patient was diagnosed with stage 3 Multiple Myeloma (MM) according to the International Staging System, and a drug regimen was initiated with bortezomib, cyclophosphamide, and dexamethasone. To evaluate the probable connective tissue disorder, Marfan syndrome *FBN1* gene sequence analysis was performed on peripheral blood by next-generation sequencing, and FBN1 NM_000138.5:c.1217T>A p.(Leu406His) heterozygous mutation was detected.

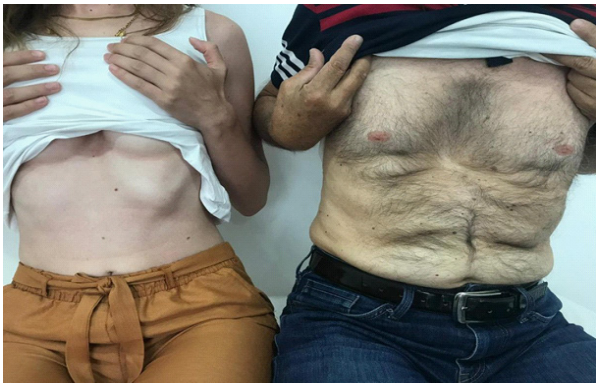

Figure 1: Barrel chest deformity in the patient and his daughter.

Discussion/conclusion

Fibrillins, especially FBN-1/2, are essential components of microfibrils that provide strength and elasticity to the extracellular matrix and are involved in maintaining the pluripotency of embryonic stem cells. They also play a role in malignant processes and are important in the regulation of members of the Transforming Growth Factor (TGF)-β superfamily [2]. TGF-β signaling also plays a role in malignant processes. TGF-β loses its antiproliferative effect in tumor cells and becomes an oncogenic factor. As a result, TGF-β function is impaired in various solid and hematological malignancies [3]. TGF-β has been linked to a variety of solid malignancies, including head and neck, bladder, prostate, colon, lung, breast, liver, and renal cell cancer. The TGFBR2 gene is a tumor suppressor gene involved in the pathogenesis of congenital connective tissue diseases and malignancies [2]. These molecular mechanisms might lead to an association of MFS with both solid tumors and several hematologic malignancies. The TGF-β/SMAD signaling pathway is constitutively activated in Natural Killer (NK) cells from patients with acute lymphoblastic leukemia and is thought to be a significant mechanism for NK cell immune escape [4]. TGF-β1 also induces the PI3K/Akt/NF-κB signaling pathway during recruitment of malignant cells in chronic myeloid leukemia [5]. Functional variants of the TGF-β1 gene are also important in the pathogenesis of AML. TGF-β1 (codon 25) GC genotype has been found to be significantly lower in AML patients than in the control group [6]. The coexistence of MFS and non-Hodgkin's lymphoma cases has been reported based on these mechanisms [7,8]. Regarding MM, TGFs have pleiotropic effects that regulate myelomagenesis as well as the emergence of drug resistance. TGF-β modulates the microenvironment, which is crucial for MM pathogenesis [9]. Although not fully elucidated, this connection may have contributed to the development of MM in our patient. To our knowledge, this is the first report that draws attention to MM-MFS coexistence.

Declarations

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Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors. This article was designed as a "Case report". Therefore, it is not required to obtain ethical committee approval.

Consent for publication: Informed consent was obtained from the patient.

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