Non-secretory myeloma in young man mimicking the Gorham disease: case report and the literature review

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Multiple myeloma is a neoplasm of plasma cells affecting mostly the elderly with incidence peaks between 60 and 70 years. This disease is exceedingly rare in younger people, especially in adults under 30-year-old. Non-secretory multiple myeloma accounts for 1–5% of all cases of multiple myeloma. It is also a rare condition in young adult patients, and only six cases have been reported [1]. We herein describe a rare case of non-secretory myeloma in a 22-year-old male, explaining from chest wall pain, without general manifestation. Plain radiography and CT scans revealed diffuse osteolytic lesion mimicking the Gorham disease. A bone marrow biopsy was conducted, revealing the diagnosis of myeloma.

Key words: multiple myeloma, Gorham disease, young people, non-secretory.

INTRODUCTION

Multiple myeloma (MM) is an age-related blood cell malignancy affecting the elderly with a median age at diagnosis of approximately 70 years. Forty percent of patients are older than 75 years [2]. Less than 2% of MM are under 40 years. This prevalence reached 0.3% in individuals younger than 30 years [3]. Clinical course, biological and radiological findings in younger and elderly MM patients were almost similar. However, survival duration and prognosis were more clearly better for younger subjects.

Non-secretory multiple myeloma (NSMM) is an exceedingly rare subset of MM. It represents only 1–5% of all myeloma and is more exceptional in young adults. Only 6 cases were reported in the literature. Their diagnosis requires bone marrow plasmacytosis detection, in the absence of monoclonal gammopathy in the serum or urine [4].

With this case report, we aim to raise awareness among clinicians about the possibility of MM in young patients.

The exceptional occurrence of NSMM in young adults makes this case worthy of illustration. Prompt disease detection will guarantee earlier

therapeutic care and improves the disease prognosis that might be rapidly fatal. To our knowledge, this is the first literature review about non-secretory MM in young patients. Herein we described clinical, biological features, and outcomes of MM in young subjects.

Case presentation

A 22-year-old male with no significant disease history complained of tenderness in the anterior chest wall and mechanical backache, evolving for seven months. Bone pain was initially diurnal and relieved with paracetamol through the first months of symptoms, worsened within the last month, becoming nocturnal and non-responding to opioids. The patient had no weakness nor fatigue. Physical examination revealed tenderness within the thoracic spine. There was not adenomegaly nor hepatosplenomegaly. The neurological examination was unremarkable.

Laboratory tests showed neither anemia nor any other cytopenia. The peripheral blood smear didn't reveal immature cell or rouleaux formation. Routine laboratory analyses were normal. Creatinine, calcium rate, and phosphate were at 10.4 mg/L, 98 mg/L, and 40 mg/l; respectively.

Inflammatory markers were normal with erythrocyte sedimentation rate at 21 mm, and C-reactive protein at 3 mg/l.

A serum proteins electrophoresis showed a slightly decreased level of gamma-globulin at 4.9 g/l. However, immuno-fixation electrophoresis in blood and urine showed no monoclonal band.

A thoracic computed tomography (CT) scan was performed and revealed a diffused lacunar osteolysis of the entire explored skeleton. The

diagnosis of Vanishing bone syndrome was suspected (Figure no.1).

A bone marrow CT-guided biopsy of the left iliac wing was finally performed. Histological examination showed an abundant hemorrhagic background with a marked plasmacytosis. The diagnostic of NSMM was concluded. The patient was referred to a hematologist and subsequently started chemotherapy with Bortezomib-dexamethasone before auto stem cell transplantation.

Figure 1. The CT scan showing the multi lacunar osteolytic lesion in sternum, ribs and spine on sagittal (a) and the 3D sequence(b).

DISCUSSION

MM is the most common malignant cell disorder in aged patients. It is characterized by the proliferation of neoplastic plasma cells within the bone marrow and the anarchical secretion of monoclonal protein [5].

The frequency of MM in younger adults is exceedingly rare, and 0.3% of cases occur in persons under 30 years [6,7]. While clinical features and outcomes seem similar to the elderly population with MM, there are some differences.

Table 1 summarized cases and series reported in the literature [7–39].

Among 123 patients with MM diagnosed at age under 30, a male predominance was striking, with a male-to-female ratio at 1.27 (M= 69). This proportion generally decreased with age-onset [5,7]. Clinical presentation was commonly silent in younger patients [6,40]. On review, the chief presenting complaints in young people were bone pain, as in the current case. However, general symptoms as weakness, weight loss, and fever were less common. Extramedullary involvement may be the first sign of disease and was found in 9 reported cases.

According to the series reported by Bladé and Nakaya, the most common CRAB symptom (hypercalcemia, renal insufficiency, anemia, bone lesion) in young MM was bone lesions. Its incidence ranges between 69% and 76% [7,39]. The contradictory calcemic rate somewhat increased.

Another biologic particularity seen in younger MM in The Jurczyszyn series was the high rate of LDH [34]. However, this finding was not found in our patient.

The M protein is used as a diagnostic tool for the clone of plasma cell identification, as a tumor marker to follow the course of the MM and response to therapy [20,41]. Similar to the elderly, MM the most frequently secreted M protein was IgG, followed by Ig A, and a light chain which was found in 41%, 45%, and 21% of series; respectively [7,39]. Nevertheless, some patients have no detectable immunoglobulin within serum or urine. In this subset of MM, the diagnosis was usually challenging, and bone marrow proof of plasma cell proliferation was mandatory. Indeed, NSMM was scarce. Its frequency varies between 1 to 5% of MM [4,42]. In the recent series, patients with NSMM were younger than those with secretory form, have fewer CRAB signs, and had less extensive bone marrow infiltration [2]. Nevertheless, NSMM in under

30 years patients is not recognized. In all reported cases, it was seen in 6 cases.

The absence of M protein and Bence Jones protein in the present patient delays diagnosis and strengthens the vanishing bone syndrome hypothesis. Interestingly, the imaging features on the chest wall and spine CT scan in our patient revealed diffuse lacunar osteolysis and cortical destruction. These findings mimic a benign osteolytic disease, especially in the absence of M protein. A similar case was recently reported by Mwanja *et al.*, in a 25-year-old female with MM [35]. In this later imaging findings in the appendicular skeleton evoked the vanishing bone disease with the lymphatic vessels' overgrowth [43]. In both of these cases, bone marrow biopsy was the discriminated diagnosis key.

A wide variety of chromosome abnormalities was identified in MM [44]. Any deletion or translocation tends to be specific for early age myeloma. Sagaster *et al* were compared these chromosomal abnormalities in three groups of MM patients aged <45 years, between 45 and 70 years, and >70 years old, and reported that all chromosomal patterns were not significantly different between the three age cohorts [45].

According to the International Staging System (ISS), stages I and II are most frequent at diagnosis time in young MM. However, stage III of the ISS is rare [6,39]. Indeed, 68% of the patients in the Jurczyszyn cohort were diagnosed in stage I of ISS [34]. Additionally, survival among young MM seems to be longer than older MM, especially in the non-secretory form [42]. This suggestion may be explained by the lack of comorbidities in the younger population and the possibility of stem cell transplantation (SCT) at this age.

Many factors may determine the treatment strategy, especially age, general health, and laboratory results [46]. In the last decade, the new treatment approach has improved outcomes in patients with MM [47]. The chemotherapy pattern used several protocols (table 1).

In the lack of specific protocol in younger myeloma, chemotherapy recommended has often been the same as the adult MM (<65 years). However, young people are eligible for high-dose chemotherapy and autologous SCT due to their age.

SCT was the most used therapeutic strategy in young MM in the Nakaya series [39]. Similar to our case, chemotherapy was initiated waiting for SCT and no accurate statement regarding its prognosis was made.

Table 1

Literature review: Clinical characteristics and outcomes of young people with plasma cell myeloma

Ref n°	Autor	Sex (or M/F sex ratio)	Age	M-protein type	Clinical presentation	CRAB symptoms				Treatment	Outcome
						Hyper- calcemia	Renal failure	Anemia	Bone lesion		
(8)	Maeda and al 1973	F	13	IgA	Breast masses with subcutaneo us nodules	No	NP	No	No	Corticosteroids +gamma- globulin+ vincristine	Death
(9)	Hewell and Alexanian 1976	M	17	IgA	knee pain and mass in the occipital area	NP	NP	No	Yes	radiotherapy in bone lesion	Chemothe rapy not required
		M	22	IgG- lambda	lymph node enlargemen t	No	No	No	Yes	MP+AD	Indolent clinical course
		M	20	NS	Diplopia and occipital mass	No	No	No	Yes	CHOP	Asympto- matic at 9 months of follow up
(10)	Clough <i>et al</i> 1977	F	24	IgG-k	Pallor, ecchymoses and renal failure	NP	Yes	Yes	No	P+AD+CA Then after two months: BCNU+MP+C	Death five months from diagnosis
(11)	Levin <i>et al</i> 1977	F	18	IgG	vision problem pregnant woman	No	NP	Yes	Yes	Local radiotherapy MP	Excellent Response
(12)	Lazarus <i>et al</i> 1980	M	22	IgG	Bone pain	Np	Np	Np	Yes	Cis + BCNU + CVP + chlorambucil	No significant Improve- ment
		M	22	IgA	Paraplegia	No	No	No	Yes	MP + radiotherapy	Failure
(13)	Bernstein <i>et al</i> 1985	F	12	IgA-k	nasopharyn geal mass	No	No	No	No	V+AD+P for 21 days then changed to M-2 protocole	Stable IgA level.
(14)	Prematillek <i>et al</i> 1987	M	12	NP	NP	NP	NP	Yes	Yes	NP	NP
(15)	Harster and Krause 1987	F	29	NS	Post partum	NP	NP	Yes	Yes	NP	NP
(16)	Rapoport and Rowe 1990	M	15	IgA-k	Bone pain Neurologic al symptoms	NP	NP	NP	Yes	CVP+M BCNU	Good response
(17)	Hermann <i>et al</i> 1990	F	28	IgD	pain in the anterior wall of the chest, thoracic spine, and right shoulder	-	-	-	Yes	NP	NP

(18)	Pajor <i>et al</i> 1991	F	27	IgG-l	Anemia Pregnant woman	No	No	Yes	NP	interferon- α MP+V	Partial remission, 2 years after treatment
(19)	Kaste <i>et al</i> 1992	M	15	IgG	bone pain	No	NP	Yes	Yes	NP	NP
(20)	Grunwald <i>et al</i> 1993	M	25	IgG-l	-	-	-	Yes	Yes	NP	NP
(21)	Badwey <i>et al</i> 1993	F	25	IgG-k	Knee pain and pathological fracture	NP	NP	No	Yes	Radiotherapy	Stable after 3 years
(22)	Ishida and Dorfman 1995	F	23	NS	lump of the head	NP	NP	NP	Yes	NP	NP
(7)	Blade <i>et al</i> 1996	6M 4F	25	light chain (5) IgD (2) IgG (2)	Extra-medullary involvement (4)	Yes (2)	Yes (3)	Yes (2)	Yes (6)	radiation therapy (4) MP (6) Second line chemotherapy (6)	Death (7)
(23)	Dubrey <i>et al</i> 2008	F	29	IgG-K	vomiting and bone pain	Yes	Yes	Yes	Yes	CTD+dexa Auto-SCT	NP
(24)	Okoli 2009	F	28	IgA	Abdominal pain and vomiting weight loss	NP	Np	Yes	No	NP	NP
(25)	Crusoe <i>et al</i> 2015	M	8	IgG-k	back pain	No	No	Yes	NP	3 cycles of VCD 3 cycles DTPACE high-dose M auto SCT	Failure Failure Partial response Partial response
(26)	Akhtar and al 2005	F	30		weakness and pain	No	No	No	Yes	MP	Improvement after 6 cycles of chemotherapy
(27)	El Mangad and al 2014	M	27	BJP lambd a light chain	bone pain	Yes	yes	Yes	Yes	CTD+dexa SCT	
(28)	Pilbeam and al 2017	M	14	IgA-k	low back pain	No	No	No	Yes	Radiotherapy systemic therapy (NP)	Good response
(29)	Radhakrishnan and al 2017	M	8	IgM	diffuse body pain, vomiting, and fever	Yes	No	Yes	Yes	P	Death
(30)	Kumar <i>et al</i> 2017	F	28	IgG	Extramedullary mass	NP	NP	Yes	Yes	surgery followed by chemo-radiation	Death after 6 months
(31)	Webber <i>et al</i> 2017	M	25	BJP kappa free light chains	infectious complication	Yes	No	Yes	Yes	VRd therapy Auto SCT	Remission after 1 year
(32)	Bellahammou <i>et al</i> 2018	F	25	IgG-k and BJP	Bone pain Asthenia	No	No	Yes	Yes	VAD	NP

(33)	Mufti and Marathe 2018	F	20	IgA	nausea, vomiting, fatigue, hemorrhages	NP	Yes	Yes	No	CyBorD	Improvement of renal function
(34)	Artur and al 2018	35 M 17 F	28 (8-30)			6	4	13	36	No therapy 11 Conventional chemotherapy (4) Chemotherapy+/- immunomodulator or +/- proteasome inhibitor (29)	5-year OS rate of 77%
(35)	Mwania <i>et al</i> 2019	F	25	IgG-k	Neurological symptoms	No	No	Yes	Yes	CyBorD radiotherapy	Good response
(36)	Van Man H 2019	F	17	IgG lambda	Bone pain	NP	NP	NP	Yes	B and dexamethasone ASCT	Good response
(37)	Khan and al 2020	F	26	NP	Fever Bone pain	Yes	Yes	Yes	Yes	CyBorD	Good response
(38)	Lee <i>et al</i> 2020	F	24	IgG-l	Neurological symptom	NP	NP	NP	Yes	CyBorD C+P+E+Cis+DA	Failure Good response
(39)	Nakaya <i>et al</i> 2020	2/1	26 (range 20-39)	IgG (11) BJP(9) IgA (3) NS (2) IgD (1)	Bone pain	Yes (1)	Yes (11)	Yes (6)	Yes (18)	auto-SCT 10 auto-SCT + allo-SCT(6) chemotherapy without SCT (5) allo-SCT (5)	Death (12)

MP: melphalan and prednisone, CHOP: vincristine, adriamycin, cyclophosphamide, and prednisone; BCNU: carmustine; CVP: cyclophosphamide, vincristine and prednisone, CTD: cyclophosphamide and thalidomide, VCD: cyclophosphamide, bortezomib, and dexamethasone; M2 protocole: vincristine+BCNU +cyclophosphamide+melphalan +prednisolone; DTPACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), VRd therapy: bortezomib-lenalidomide-dexamethasone ; VAD: vincristine, doxorubicin, and dexamethasone; CyBorD: Cyclophosphamide, bortezomib and dexamethasone
AD: adriamycin (doxorubicin); CA: cytosine arabinoside (Cytarabine); B: Bortezomib; C: cyclophosphamide; Cis: cisplatin; D: doxorubicin; DA: daratumumab; E: etoposide; M: melphalan; P: prednisolone; MP: melphalan and prednisolone; BJP bence jones protein, NP: not precised; NS: non secretory; SCT: stem cell transplantation; T: thalidomide ; V: vincristine

CONCLUSION

NSMM is a rare entity in young patients (<30 years). A sternal puncture or a bone marrow biopsy is mandatory when any biological or radiographic signs evoke a MM. In front of

alarming symptoms such as osteolytic lesions or hypogammaglobulinemia, the clinician must strive to depict marrow bone infiltration with malignant cells, even in the absence of blood and urinary secretion.

Mielomul multiplu este o neoplazie a plasmocitelor ce afectează populația vârstnică, având un vârf de incidență între 60 și 70 de ani. Este foarte rară la pacienții tineri, mai ales la cei sub 30 de ani. Mielomul multiplu non-secretor reprezintă 1–5% din totalul mieloamelor și au fost raportate numai 6 cazuri în literatură. Prezentăm cazul unui pacient de 22 de ani, cu durere toracică și fără manifestări generale. CT-ul vizualizează leziuni difuze osteolitice ce mimează boala Gorham. Puncția biopsie medulară a tranșat diagnosticul de mielom.

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