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Case Report

Plasma cell leukemia about four cases

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Abstract: Plasma cell leukemia (PCL) is a rare and aggressive plasma cell neoplasm that may either originate de novo (primary PCL) or by leukemic transformation of multiple myeloma (MM) to secondary PCL (sPCL). It is defined by the presence of >2 G/L plasma cells or >20% plasmacytosis of the differential white cell count in the peripheral blood. In this case series, we describe the clinicopathologic, biologic and immunophenotypic, of four patients diagnosed with PCL within a four years period (2013-2016) at CHU Hassan II, Fès, Morocco**.**

Keywords: Plasma cell leukemia (PCL), multiple myeloma

INTRODUCTION

Plasma cell leukemia (PCL) is a rare and aggressive lymphoproliferative disorder characterized by high levels of malignant plasma cells in the peripheral blood [1]. It is defined by the presence of more than $2x10^9$/L peripheral blood plasma cells (PC) or plasmacytosis accounting for >20% of the differential white cell count. Primary PCL is malignant PC proliferation that is first diagnosed in the leukemic phase, while secondary PCL corresponds to the leukemic transformation of a previously diagnosed multiple myeloma (MM) [2]. Gene expression profiling suggests that the two forms constitute separate molecular entities [3]. PCL is associated with poor prognosis, with a median overall survival (OS) of only seven months [4]. In this case series, we describe the clinicopathologic, biologic and immunophenotypic of four patients diagnosed with PCL within a four years period (2013-2016) at CHU Hassan II, Fès, Morocco.

CASES REPORT

Case 1

A 58-years old mal patient was refered in September 2013 with severe anemia and Haemorrhagic syndrome made of epistaxis and gingivorrhagia. On physical examination, patient looked pale. A submandibular lymphadenopathy was detected. Abdominal pain elicited by superficiel and profound palpation but no signs of peritonitis; absence of hepato-splenomegaly. His skeletal survey and abdominal ultrasound were normals. A complet blood count at the time of referral showed a white blood cell (WBC) count of $21x10^9$/L with 75% circulating plasma cells, HBG level of 68g/L and platelet count was $22x10^9$/L. The biochemical profile was: serum creatinine 15 mg/l, urea 0.3 mg/l, calcium 102mg/L, lactate dehydrogenase test (LDH) 427 U/L, serum β2 microglobulin 15 mg/L, C reactif protein (CRP) 13 mg/L. Serum protein electrophoresis (SPE) revealed hypogammaglobulinemia and urin protein electrophoresis (UPE) was negative. The bone marrow (BM) was infiltrated with 80% plasma cells, with CD38+, CD138+, CD20+, CD56-. Cytogenetic analysis could not be carried out. Patient died with septic shock before starting treatment.

Case 2

A 42-years old male patient was diagnosed as a case of stage III IgA lambda MM. He received Tahlidomide-prednisone-zometa and was refered in july 2012 for evaluation and treatment of MM. Physical examination did not show hepato-splenomegaly nor lymphadenopathy. His skeletal survey demonstrated collapsed L5 vertebral. Abdominal ultrasound was normal. Laboratory tests showed elevated level of calcium blood and B2microglobulinemia. SPE and immunofixation revealed IgA-Lambda with gamma globulin spike 66.1 g/l, and 389g/l of IgA. Urinalysis was positive for Bence Jones protein (BJ protein). Because of his young age, hypercalcemia and high level of B2microglobulin, decision was to start VAD chemotherapy (vincristine, adriamycin, dexamethason), CMVP (oncovin, melphalan,endoxan,cortancyl) and DCEP (dectancy, cisplatin, etoposide, endoxan) in second intention. After two years, patient presented epistaxis and multiple body hematomas. Laboratory

tests revealed pancytopenia: white blood counts of 4,2x 10^9/L with 32%the peripheral blood smear showed circulating plasma cells, HGB level of 52 g/L, and platelets were 18x10^9/L. The biochemical profile was: serum creatinine 34mg/l, urea 0.93 mg/l, GOT 82U/L, GPT 43U/L, hypercalcemia 110 mg/l, LDH 905 U/L, and B2 microglobuline 4,3 mg/l. BM demonstrated diffuse involvement by 82% of PCs CD38+, CD138+, CD56+ immunophenotype. FISH was positive for deletion of 17p. The patient received CDT (Endoxan Thalidomide Dexamethasone) chemotherapy as his disease evolved to sPCL, and doses of erythropoietin. He died 14 months after diagnosis of leukemia.

Case 3

A 60-years old female patient presented in February 2016 with symptoms including couthing, shortness of breath and generalized weakness. She was known to have hypertension. Physical examination showed a patient with tachypnea, tachycardia and lower extremity edema, no evidence of organomegaly was detected. Laboratory tests revealed a high level of D-dimer testing (2904 ng/ml). Pulmonary angiography confirmed central pulmonary embolism. In other side, hematology exam showed a WBC count of 36x10^9/L with 20% circulating PCs, HGB level of 88 g/L and PLT count was 65x10^9/L. The biochemical profile was: blood creatinine 32 mg/L, urea 0.55 mg/L, calcemia 88 mg/L, LDH 698 U/L, and B2-microglobulin 11,6 mg/L. SPE revealed a gamma monoclonal spike. Immunofixation showed a spike of IgG kappa. Serology HIV was negative. BM showed diffuse infiltration by 53% of PCs, which were large, nucleated with prominent nucleoli (figure 1). Flow cytometry showed that cells were positive for CD38, CD138, CD20, CD79a, while negative for CD56. Skeletal survey showed generalized osteopenia. Diagnosis of pPCL was confirmed. Cytogenetic analysis didn't reveale cytogenetic abnormalities. Because of her age, comorbid disease (pulmonary embolism), patient received VTD (velcade, thalidomide, dexamethason) and unfractionated heparin. She was lost to follow up.

Case 4

A 66-years old male patient was admitted in November 2016 with shortness of breath, hemoptysia, severe anemia, generalized weakness, and loss of weight. Five months ago, he started with knee and low back pain which was resistant to non steroidal anti inflammatory drugs. He had no comorbidities but smoked 10 cigarettes daily during 52 years. On physical examination, patient was pale dyspneic; no evidence of organomegaly was detected. There was pain during mobilization of hip. Radiograph chest showed pulmonary nodules. Skeletal survey and RMI showed multiple lytic lesions in lumbar vertebria (figure 2). Laboratory studies revealed a WBC count of 15.7 x10^9/L with 40% circulatins PCs, HGB level of 93 g/L and PLT count was 83x10^9/L. Serum creatinine was 17 mg/L, B2 microglobuline 14.4 mg/L, and LDH 144 U/L. SPE revealed gamma monoclonal spike. Immunofixation showed a spike of IgG kappa. Benes jones protein was positive. Bone marrow smears showed features consistent with diagnosis of multiple myeloma (MM). Flow cytometry confirmed that 58% plasma cells were CD38+, CD138+, CD54+, and CD56+. Cytogenetic analysis revealed complex karyotyping of -13,-14, t(4,14), 46 XY. The patient received VDT and died from refractory plasma cell dyscrasia progression, one month after diagnosis of PCL.

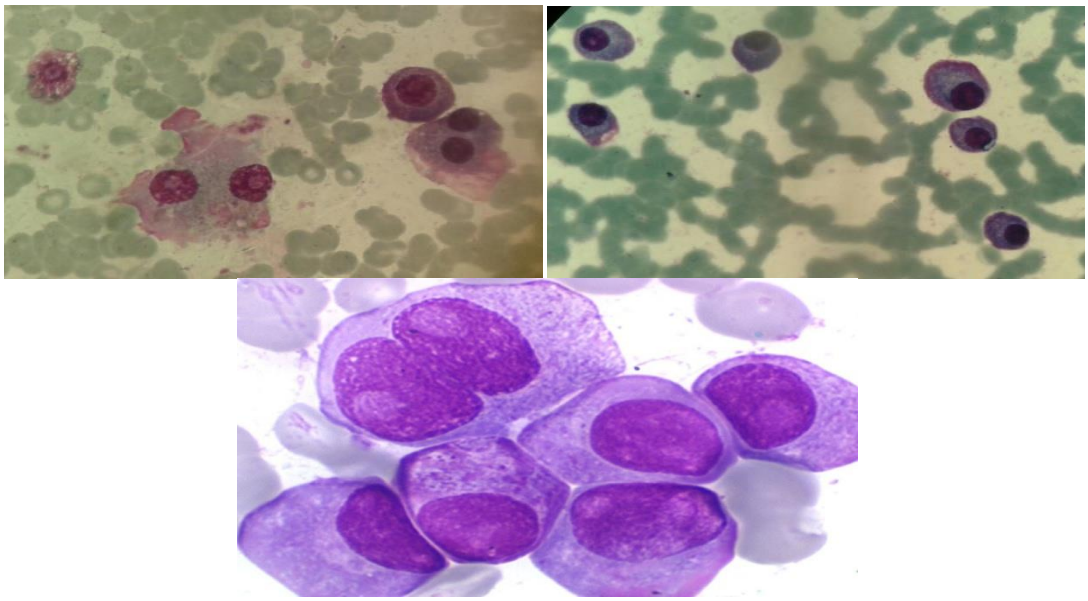

Fig-1: Apparence of Bone marrow at diagnosis: presence of a plasma cells infiltration in approximately 20%, cells with eccentric round nucleus and condensed chromatin, some of them multinucleated, basophilic cytoplasm. MGG stain, ob. 100×

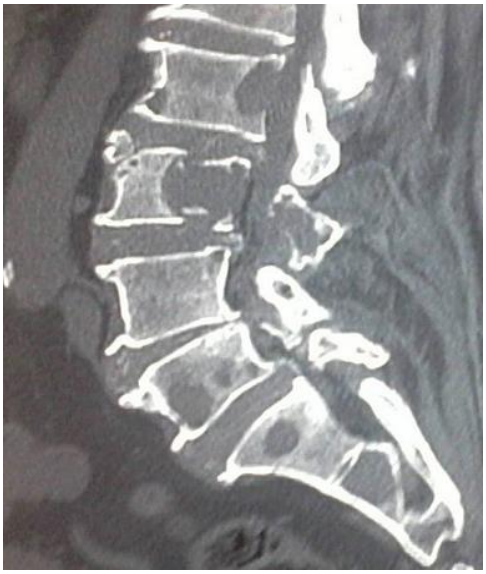

Fig-2: Multiple osteolytic lesions in the lumbar spine.

Table-1: Characteristics of the four PCL patients.

	Case 1	Case 2	Case 3	Case 4	Median
PLC type	Primary	secondary	primary	Secondary	
Sex	Male	Male	Female	Male	
Age (y)	58	42	60	66	56.6
Organomegaly	Lymphadenopaty	No organomegaly	No organomegaly	No organomegaly	
Bon lesion	No osteolytic lesions	Multiple lytic lesions	Diffuse osteopenia but no osteolytic lesions	Multiple lytic lesions	
Ca total (mg/l) N (88-108)	102	110	88	132	108
Creatinine (mg/l) N (6-11)	15	34	32	17	24.5
LDH (U/L) N (0-243)	427	905	698	144	543.5
Seum Protein electrophoresis	Hypogammablobulinemia	IgA lambda	IgG kappa	IgG kappa	
Urine protein electrophoresis	No proteinuria	IgA lambda	No proteinuria	free kappa light chain monoclonal gammapathy	
B2 microglobulin (mg/l) N (0,8-2,4)	15	4.3	11.6	14.4	11.3
WBC (10^9/L) N (4-10)	21	4.2	36	15.7	19.2
Hg (g/dl) N(12,5-15,5)	6.8	5.2	8.8	9.3	7.5
PLT (10^9/L) N(150-400)	22	18	65	83	47
PCs in PB (%)	75	32	20	40	41.75
PCs in BM (%)	80	82	56	58	69
Immunophenotyping	CD38+, CD138+, CD56-	CD38+, CD138+, CD56+	CD38+, CD138+, CD20+, CD79a+, CD56-	CD38+, CD138+, CD54+, CD56+	

PCL: plasma cell leukemia; y: year; Ca: Calcium; N: normal; LDH: Lactate Dehydrogenase; NA: not available.

Table-2: Immunoglobulin Classes in three series of PCL

	Dimopoulos and al. 1994	Garcia Sanz and al.1999	Costello and al. 2001
IgG	52%	54%	27%
IgA	15%	4%	22%
Light chains	26%	31%	27%
Non secretive	7%	4%	17%
IgD	-	8%	-

IgM	-	-	5%

Table-3: incidence of major clinical and biological characteristics in pPCL and sPCL

	pPCL	sPCL
extramedullary disease	++++	Less than 20%
Bone lytic lesions	25%	90%
Bone pain	40-60%	70%
Infections	35%	56%
Platelets	50%	71%

Table-4: Comparison of bone marrow plasma cell immunophenotyping in Plasma Cell Leukemia and Multiple Myeloma

Immunophenotype	Plasma cell leukemia	Multiple Myeloma.
CD138+	100%	100%
CD11a+	19%	91%
CD18+	26%	89%
CD29+	94%	100%
CD38+	100%	100%
CD44+	83%	63%
CD49d+	100%	100%
CD54+	93%	81%
CD56+	pPCL 45% Spcl 75%	66%
CD71+	30%	60%
CD1177+	27%	31%

Table-5: Comparaison of immunophenotypic markers in MGUS, MM, pPCL, sPCL

	Monoclonal gammapathy of undeterminated signification (MGUS)	Multiple myeloma	Secondary Plasma cell leukemia	Primary plasma cell leukemia
Adhesion molecule				
CD138	NC	+++	+++	+++
CD38	+++	++	+	+
CD56	+++	+++	++	+
Response immune				
HLA1	+++	++	+	NC
CD40	+++	+++	+	NC
CD20	NC	+	NC	++
CD117	NC	++	0	0
HLA-DR	NC	++	NC	+

Table-6: Cytogenetics data available in plasma cell leukemia series

Cytogenetics abnormalities (%)	Garcı´a-Sanz et al. [5]	Dimopoulos et al. [4]	Tiedemann et al.[7]	Pagano et al.	Avet-Loiseau et al.	Chiecchio et al.
Hypodiploidy		41	60	12.2	47	41.6
Hyperdiplody			0	4.9	8.8	33.3
Complex karyotype		92	54.4	34.2	58.8	66.7
del(13q14) or monosomy	84	50	85	19	68	58
del(17p13)			50	7.3	11.8	25
t(11;14)			71	19.5	33	42
t(4;14)			0	0	12	8.3
t(14;16)			0	0	16	25

DISCUSSION

Plasma cell malignancies include four entities: classic MM, extramedullary plasmacytoma without MM, solitary plasmacytoma of bone, and PCL [1]. PCL represents between 2 and 4% of this group of patients, and 0.3% of acute leukemias [1, 5].The overall incidence rate in Europe of all PCL is approximately 1 case per 2.5 million persons/year, and of these generally 30-40% constitutes sPCL [3]. In Morocco, the Rabat Cancer Registry shows that the incidence of MM in 2005 was 22 per million persons/year for men and 9.4 per million persons/year for women [6]. These figures give us an approximate estimate of PCL in our context, as it complicates 2-4% of MM. The clinical and laboratory results for all four cases are summarized in Table 1. Two out of the four cases were primary PCL and two cases were secondary. It has been reported that male to female sex distribution in both primary and secondary PCL are (3:2) [2]. The male to female ratio was equal (3:1) in our patients and the age range was 42-66 years. Patients with PCL tend to present with aggressive clinical features, such as associates asthenia, bone pain, anemic syndrome and hemorrhage, extramedullary disease, bone marrow failure, advanced stage disease. Up to 15% of PCL patients will have extramedullary involvements, mainly hepatic (52%) and splenic (40%) [7]. One out of our four patients had lymphadenopathy, where none of the patients showed hepatomegaly and/or splenomegaly. Bone lytic lesions were observed in two cases. One patient had a generalized osteopenia.

Because of extensive involvement of the bone marrow, they tend to show a higher prevalence of cytopenia. This is evident in all of our patients with 75g/L and 47.10^9/L median hemoglobin level and platelets counts, respectively, at diagnosis [2, 8].

Other laboratory findings include a higher prevalence of renal insufficiency (80 to 100% of pPCL), hypercalcemia (44%) elevated b2-microglobulin (65-91%) and elevated LDH (60%) [9]. Our four cases had renal insufficiency; the four tested patients showed high b2-microglobulin; and three out of four tested cases revealed high LDH.

PCL is usually diagnosed by staining a peripheral blood smear with May Grunwald Giemsa to detect Plasma cells>2G/L or >20% of total leukocytes. BM biopsy typically demonstrates extensive involvement by PCs that disrupt the normal hematopoiesis.

In some cases, the tumor cells resemble normal plasma cells with basophilic cytoplasm, prominent Golgi zone, and eccentric nuclei. Yet others have more primitive cells with a higher nuclear cytoplasmic ratio, open chromatin, prominent nucleoli, and a less prominent Golgi zone (plasmablasts) as in case 4 [10]. Sometimes, circulating plasma cells are difficult to classify by light microscopy alone, and differentiation from other conditions requires immunophenotypic analysis, which can also be useful to differentiate reactive from clonal plasma cells.

PC secretes a complete immunoglobulin or light chains found in 39% of cases with 50% of case the lambda isotype. Non secretory PCL were reported [9] (Table 2). All four cases expressed monotypic cytoplasmic immunoglobulin light chain.

Secondary form of PLC complicating a known MM is easily diagnosed. In Table 3 we compare the incidence of major clinical and biological characteristics in pPCL and sPCL [9].

Flow cytometry analysis using CD38 and CD138 antigen expression is an excellent PC marker. Kraj and al compared flow cytometric immunophenotypic characteristics of 36 cases of plasma cell leukemia (23 primary, 13 secondary) and 47 MM patients. Tumor cells from PCL patients have reduced expression of the adhesion molecules NCAM (neural cell adhesion molecule/CD56) and LFA-1 (leukocyte function-associated antigen-1), which may contribute to the extramedullary accumulation of tumor cells in PCL [8, 13]. Immunophenotypic profiles of primary and secondary PCL were comparable, except for CD56 expression, which was more often present in secondary PCL (Table 4). The International Myeloma Working Group [7] proposed discriminating markers in difficult diagnosis and follow up of PCL (Table 5).

The molecular basis of PCL is poorly understood. Cytogenetic studies show that plasma cells in pPCL have a number of genetic abnormalities. More than 80% of patients with PCL have hypodiploid or diploid cells, which is associated with poor prognosis, whereas about 60% of patients with MM display hyperdiploidy, a favorable finding. Five chromosomal abnormalities in PCL are summarized in Table 6. Results of these studies are very heterogeneous, basically based on retrospective studies and unsorted samples [11].

PCL is an extremely aggressive disease with no standard treatment regime so far due to the rarity of the disease. Melphalan/Prednisolone (MP), infusional Vincristine, Doxorubicin and Dexamethasone (VAD) or Thalidomide/ Dexamethasone (TD) regimes have been tried but the outcome has been dismal. Prognosis is generally very poor with a median survival of 2–8 months. The impact of newer agents, such as Bortezomib and Lenalidomide, in conjunction with autologous and allogeneic stem cell transplantation is uncertain, but emerging data suggest that use of these

modalities may help improve the poor prognosis of patients with PCL [12].

CONCLUSION

PCL has been scarcely reported due to very low frequency; therefore, therapy remains not consensual. The secondary type of PCL is frequently resistant to chemotherapy including agents used against MM; primary PCL also has poor prognosis in spite of multiple drug regimens, and needs stem cell rescue. The morphology of the plasma cell could be highly misleading, and for that reason, comprehensive workup by immunophenotyping using flow cytometry is crucial for the diagnosis of PCL. More case reviews are required to reach a better understanding of the pathogenesis of PCL.

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