



Case Report

Aberrant Acquisition of T-cell Associated Markers in Plasma Cell Neoplasms: An Aggressive Disease with Extramedullary Involvement and Very Short Survival

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Abstract. Background: Plasma cell neoplasms can show aberrant expression of different lineage-related antigens; however, co-expression of T-cell-associated markers on malignant plasma cells is extremely rare.

Material and methods: This report describes clinicopathologic characteristics of three myeloma patients with emergent plasmablastic morphology and aberrant acquisition of T-cell-associated markers diagnosed in our center. An extensive literature search for similar cases was conducted, and the relevant pathologic, clinical, and prognostic characteristics were summarized.

Results: A total of 22 cases of plasma cell neoplasm (including the three cases reported here) showed aberrant co-expression of T-cell markers. We found an evident association between aberrant expression of T-cell markers on malignant plasma cells and extramedullary involvement, aggressive morphologic features, high proliferative index ki67 >90%, aggressive clinical course, an adverse outcome, and short survival.

Discussion & Conclusion: Due to the rarity of this aberrant phenotype and scarcity of the published data, the precise causative mechanism and its clinical implications have not yet been elucidated.

Keywords: Aberrant T-cell markers; Plasma cell myeloma; Plasma cell neoplasm; Aggressive myeloma.

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Introduction. Plasma cell neoplasms (PCN) is a clonal expansion of immunoglobulin secreting, terminally differentiated mature effector B-cells that classically secrete a single homogeneous monoclonal

immunoglobulin (M protein).¹ PCN can show aberrant expression of different lineages related to antigens, but the expression of T-cell associated markers is exceedingly rare. Herein, we describe three patients with plasma cell myeloma (PCM) who relapsed with an aggressive disease with plasmablastic morphology, extramedullary involvement, high ki-67, and complex karyotype. Interestingly, these patients showed aberrant acquisition of single or multiple T-cell associated markers, and two of them died shortly after their latest presentation. Due to the rarity of this aberrant phenotype and scarcity of the published data, the precise causative mechanism and its clinical implications have not yet been elucidated. Multiple theories have been proposed to explain the aberrant expression of T-cell markers on plasma cells (PCs), being terminally differentiated cells. Lineage infidelity is uncommon in terminally differentiated B-cell lymphomas. An extensive literature search for patients with similar findings was conducted, and the relevant pathologic, clinical and prognostic

characteristics were summarized.

Methodology. This report describes three myeloma patients with emergent plasmablastic morphology and aberrant acquisition of multiple T-cell associated markers diagnosed in the National Centre for Cancer Care and Research (NCCCR) in Qatar. The aberrant co-expression of T-cell associated markers is confirmed by both flow cytometry (FCM) and immunohistochemistry (IHC). Herein, we are documenting the detailed clinicopathologic characteristics and cytogenetics features of these patients. In addition, we conducted a systematic literature search using PubMed, Google Scholar, and Scopus for patients with plasma cell myeloma/ Plasma cell neoplasms and aberrant T-cell expression, using pre-defined search terms and synonyms.

Results. *Results of Patients diagnosed in our center (Table 1, first three cases).*

Table 1. Clinical, morphologic, immunophenotypic and cytogenetics features of cases of plasma cell neoplasm with aberrant expression of T-cell associated markers.

	NO/Age/Sex	Denovo/Relapsed latency period	Involved sites at relapse	Morphology/KT	Plasma cell Phenotype	Aberrant marker expression	Aberrant T-cell antigens	Other Markers	Treatment before relapse	Response
Case 1	47/M	Relapse/ 2 Mo	Skin nodules (chest wall)	Plasmablastic Anaplastic Mitosis++ <i>Complex KT</i>	CD38+ CD138+ IgD/L CD45+ CD19- CD20-	CD56-, CD117- CD10+ (dim) CD33+	cCD3+ P CD4+ CD7 P	C-MYC+ Ki 67 >95% P53 - CD30 - EBER-	VRD, A SCT	Renal failure expired in 2 MO
Case 2	56/M	Relapse/ 5 y	Multifocal spinal, chest wall, axillary	Plasmablastic Fibrosis ++ <i>Complex KT</i>	CD138 P CD38+ IgG/K CD45+ CD19- CD20-	CD56+ CD117 P CD10 P CD33 P CD79bP	CD4+	C-MYC+ Ki 67 >95% P53+ CD30- EBER-	VCD ASCT	Progressed, expired in 3 MO
Case 3	66/M	Relapse 2 years	Pleura, LN	Plasmablastic Mitosis++	CD138+ K CD19- CD20-	CD56- CD117- CD10 P	cCD3+ cD7+	C-MYC+ Ki 67 >70% P53 - CD30- EBER-	Progressed	
Case: 4-9 [7]	Six patients from a total population of 215 samples of plasmacytic malignancies expressed T-cell associated antigens, four patients expressed T-helper antigen (CD4), One expressed CD3, and one expressed CD2. Five cases showed aberrant T-cell antigen at relapse.									
Case 10 [11]	69/M	Relapse/ 7.5 months	Liver	Plasmablastic	IgA, K	NA	CD3+		VAD	Died 4 days after diagnosis
Case 11 [19]	M/64	Relapse/ 4 months	bone, muscle, LN, soft tissue	plasmablastic myeloma	CD138+ CD20-	CD56+ CD10+ Cyclin D1-	CD3+	EBER+ KI-67 >80%	NA	NA
Case 12: [22]	M/60	NA	Neck, skin, thorax	Plasmablastic transformation	CD138 K CD20-	CD30-	CD3+	EBV-	NA	NA
Case 13: [22]	M/48	NA	Sacrum Plasmacytomas		CD138+ L	CD10-	CD3+	NA	NA	NA

					CD20-					
Case 14: [22]	M/59	NA	BM	Anaplastic Myeloma	CD138+ K CD20-	NA	CD3+	EBV-	NA	NA
Case 15: [22]	M/57	NA	Sacrum Plasmacytoma		CD138+ K CD20- CD19+	CD30-	CD3+ P	EBV-	NA	NA
Case 16 [23]	60/F	Relapsed	LN	Immunoblast-like cells with prominent nucleoli. Brisk mitosis. FISH: cMYC -	CD38+ CD138+ Free K CD20- PAX-5-	CD56+ cyclin D1-	CD3+ CD4+	cMYC- KI-67 >95% CD30 - EBER -	VCD Radiotherapy	Lost follow-up after 16 MO
Case 17 [24]	M/54	Relapse/ 4 years	BM	Complex KT with clonal evolution, TP53 mutation	CD138+ K	CD56+ cyclin D1	cCD3+ CD2P+ CD7P+ CD8P+	EBER - CD30 -	Lenalidomide dexamethason	Progressed to PCL & died in 3 MO
Case 18 [25]	67/F	At diagnosis	Solitary Iliac mass plasmacytoma		CD138+ IgG/L	CD19- CD20 CD117- Cyclin D1+	cCD3+ CD4+ dim	EBV-	NA	NA
Case 19 [26]	37/M	At diagnosis	PB BM	PCL 17p13 del FGFR3/IgH	CD138- CD19+ IgD+ CD79b-	CD56- CD117- BCL-2+ BCL-6+	CD4+			NA
Case 20 [27]	M/67	NA	Radius	NA	CD20-	CD10-	CD3+	EBV-	NA	NA
Case 21 [28]	62/M	At diagnosis	Mandibular mass	Plasmablastic numerous mitotic figure	CD138+	CD56+ CD20-	CD3+ CD4+	CyclinD1 + EBER -		NA
Case 22 [29]	48/M	At diagnosis	Skin nodules LNs	Plasmablastic	CD138+ L	CD56+	CD3+ CD4+	c-MYC CD30- EBER- KI67: >90%	Brotozomib dexamethase Oxorubicin	Died shortly after first cycle

Abbreviations: Years (Y), Months (MO); Male (M); Female (F), Plasma cell leukaemia (PCL), Positive (+); Negative (-), Partial(P), Lymph node(LN); Peripheral blood (PB); Bone marrow (BM), Kappa (K), Lambda (L); autologous stem cell transplantation (ASCT).

Case 1. A 47-year-old male presented with multiple painless subcutaneous swellings on the trunk, abdomen, and thigh, associated with significant weight loss with no fever or night sweats. Serum protein electrophoresis (SPE) showed two bands; IgD lambda and free lambda. Free light chain (FLC) lambda was remarkably increased 1296 mg/L (5.71 - 26.30) with Kappa/Lambda (K/L) ratio of 0.01 (0.260 - 1.650). Skin biopsy confirmed involvement by PCM with Lambda light chain restriction and expression of BCL2 and c-MYC. FISH analysis was negative for C-MYC, BCL2, BCL6, 17p deletion, and 14q32 rearrangements.

Bone marrow (BM) examination confirmed the diagnosis of IgD-PCM; the plasma cells mainly were mature looking mixed with few atypical forms, negative for CD45, CD20, CD117, and CD56 with no immunophenotypic aberrancies detected. The patient started on VRD chemotherapy (Bortezomib 1.5mg/m² weekly/lenalidomide 25 mg for 21 days/Dexamethasone 20mg weekly) every 28 days cycle given for four cycles with complete resolution of skin nodules. Then he underwent an Autologous stem cell transplant (ASCT).

Two months later, the patient developed new skin nodules in the upper chest wall and found a right renal mass. Peripheral blood (PB) revealed rare circulating PCs detected on screening of peripheral smear. BM at relapse revealed infiltration with many myeloma cells (78%) showing marked pleomorphism including many forms with plasmablastic and anaplastic morphology and increased mitotic figures (**Figure 1; A and B**). FCM (**Figure 2**) showed a large population of lambda restricted monotypic PCs showing variation in forward scatter (cell size), and side scatter (cytoplasm complexity) and expressing CD45, CD38, CD138, dim CD10 with aberrant expression of CD33 and CD4 with aberrant partial expression of CD7 and cytoplasmic CD3. PCs were negative for CD19, CD20, CD117 & CD56. By IHC (**Figure 3**). The PCs were Lambda restricted and expressed cMYC, BCL-2 with confirmed aberrant expression of CD4 and partial expression of CD7 and CD3. The PCs were negative for CD20, CD56, CD117, P53, and EBV. The myeloma cells showed a very high mitotic index reflected by KI-67 >90%. Cytogenetics studies revealed complex karyotype: 47,X,Y, i(1)(q10),

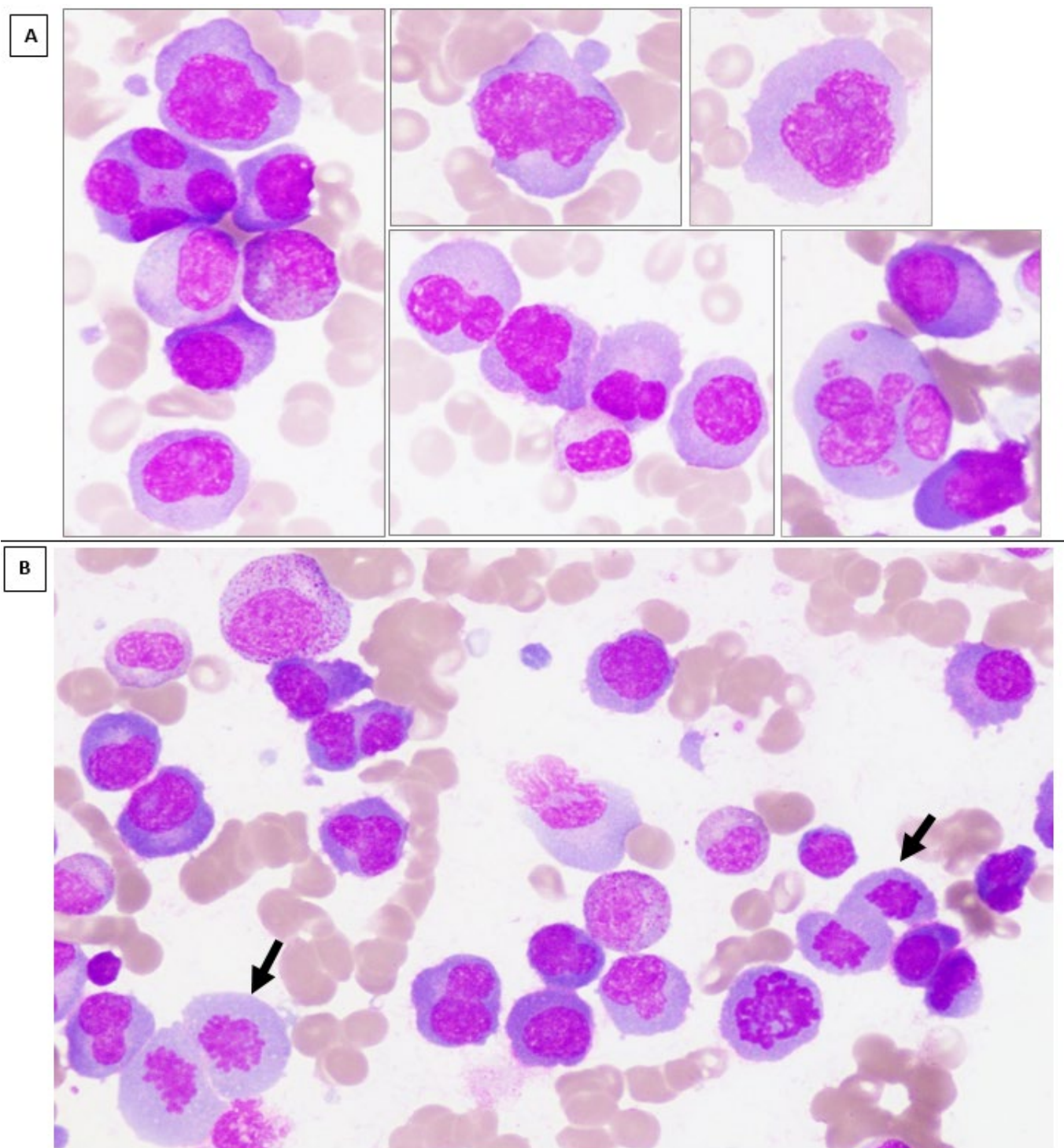


Figure 1. Case (1): BM aspirate at relapse (100x) revealed extensive infiltration with many myeloma cells showing marked pleomorphism including many forms with plasmablastic and anaplastic morphology (with marked nuclear irregularities) (A and B) and increased mitotic figures (B, black arrows).

t(1;3)(p32;p13), +der(3)t(1;3)(p32;p13), add(4)(q35), der(8)t(8;15)(q24;q11.2) add(8)(p23), add(13)(q34), +20.²⁰

PET/CT showed multiple intramedullary lesions in bilateral humerus and femur, multiple newly developed FDG-avid subcutaneous nodules in the right upper chest wall, and right renal lesion (**Figure 4**).

The patient was started on second-line treatment (Carfilzomib 20 mg/m²) for two days; unfortunately, he

progressively deteriorated and passed away.

Case 2. A 56-year-old male presented with lower limb numbness with spinal plasmacytoma (at T4 level) and 22 % clonal plasma cells in the BM, confirming PCM diagnosis.

The patient underwent decompressive laminectomy and local radiotherapy followed by Lenalidomide (25 mg for 21 days every 28 days cycle) with dexamethasone for

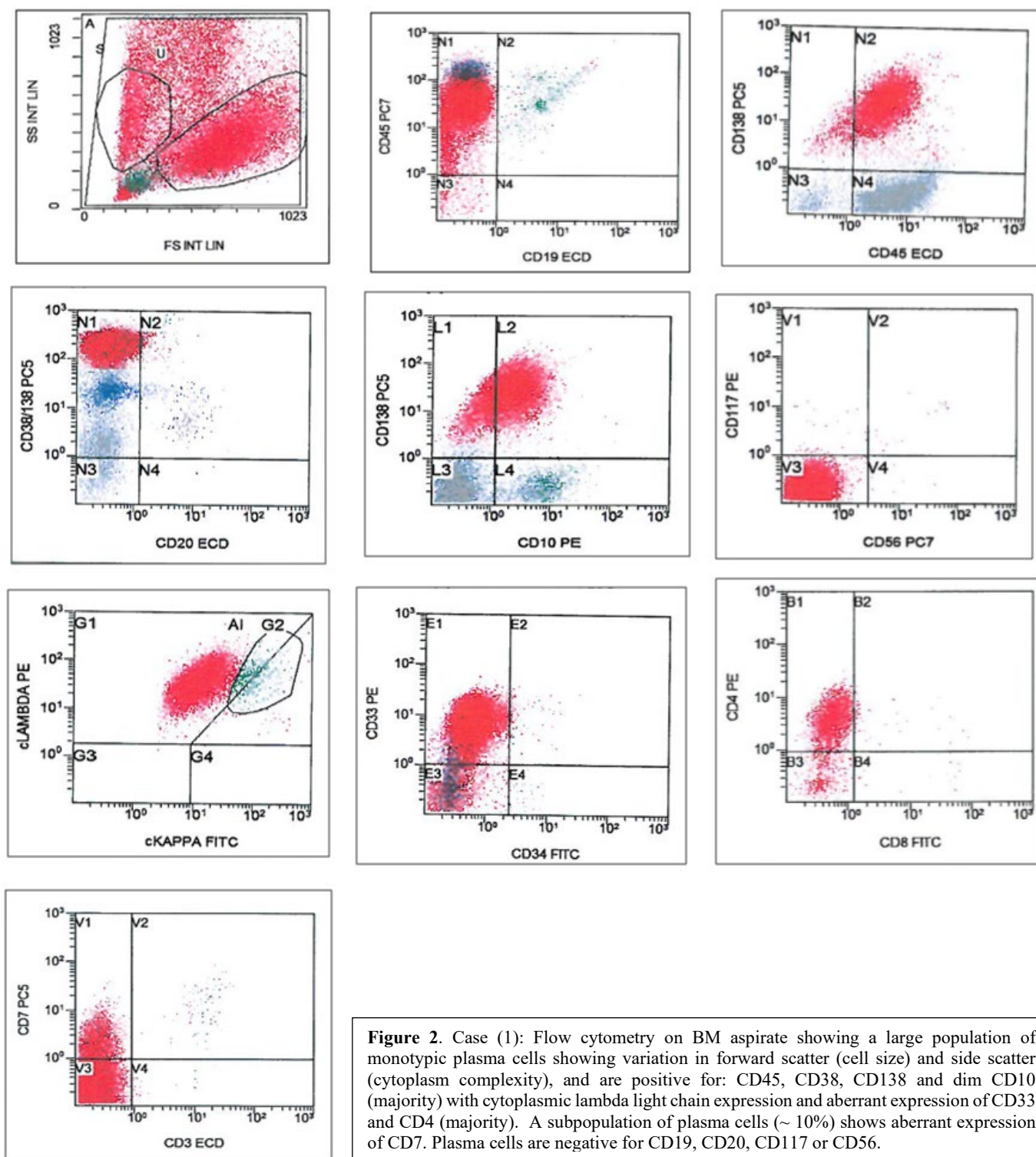


Figure 2. Case (1): Flow cytometry on BM aspirate showing a large population of monotypic plasma cells showing variation in forward scatter (cell size) and side scatter (cytoplasm complexity), and are positive for: CD45, CD38, CD138 and dim CD10 (majority) with cytoplasmic lambda light chain expression and aberrant expression of CD33 and CD4 (majority). A subpopulation of plasma cells (~ 10%) shows aberrant expression of CD7. Plasma cells are negative for CD19, CD20, CD117 or CD56.

12 cycles, and he achieved complete remission.

Four years later, he relapsed and retreated with Lenalidomide-dexamethasone for 7 cycles with partial response, then he was started on VCD (Bortezomib - Cyclophosphamide-Dexamethasone), followed by ASCT and achieved a second complete remission, but no maintenance was given.

Sixteen months later, he relapsed and was started on Carfilzomib-Dexamethasone, but he progressed while on therapy with multifocal spinal lesions, right chest wall, and axillary masses when he was treated with

Pomalidomide and Daratumumab. However, he progressed with a newly developed scalp mass lesion.

At his latest presentation, SPE and immunofixation showed IgG kappa monoclonal band (20.9 g/L), Kappa FLC was markedly increased at (1227mg/L), with a high K/L ratio at 204.5.

The BM was infiltrated by many myeloma cells with plasmablastic morphology. FCM on BM showed monotypic PCs (53%), with variable forward and side light scattering, expressing CD45 and with a heterogeneous expression of CD138 and CD38 with

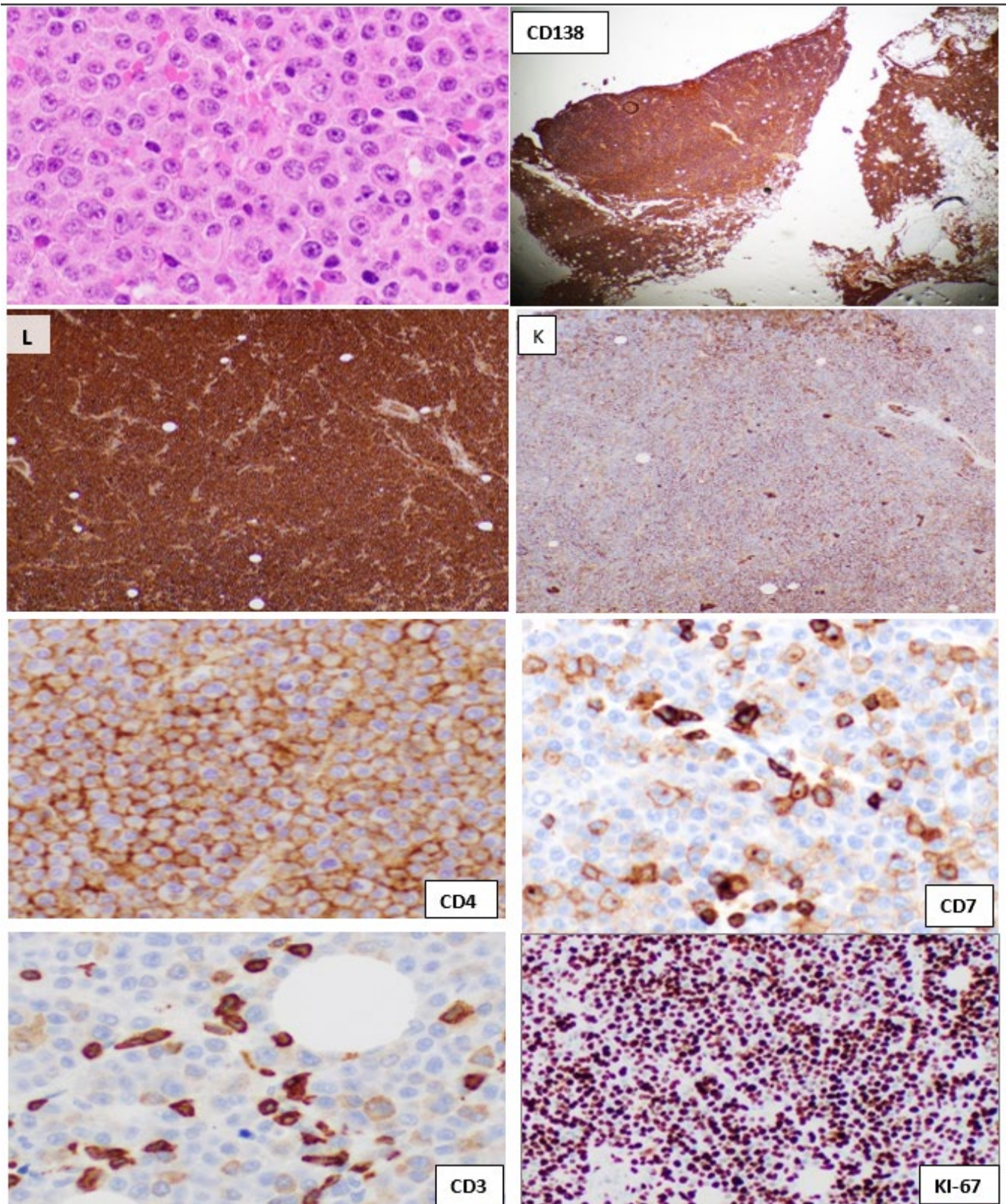


Figure 3. Case (1): BM biopsy (H&E; 50x) (A): showing extensive infiltration by myeloma cells of plasmablastic morphology with prominent nucleoli. By IHC: The PCs were Lambda restricted (B), negative for Kappa (C) with aberrant expression of CD4 (D) and partial expression of CD7 (E) and CD3 (weak positive cells) (F). The myeloma cells showed a very high mitotic index reflected by KI-67 >90% (G).

cytoplasmic kappa light chain restriction and aberrant expression of CD56 and CD4. In addition, there was a partial expression of CD10 and CD79b and aberrant partial expression of CD117 and CD33. This monotypic

population is negative for CD19 and CD20.

BM biopsy was hypercellular (90-95%) with extensive and diffuse infiltration by sheets of abnormal kappa-restricted monotypic PCs, which by

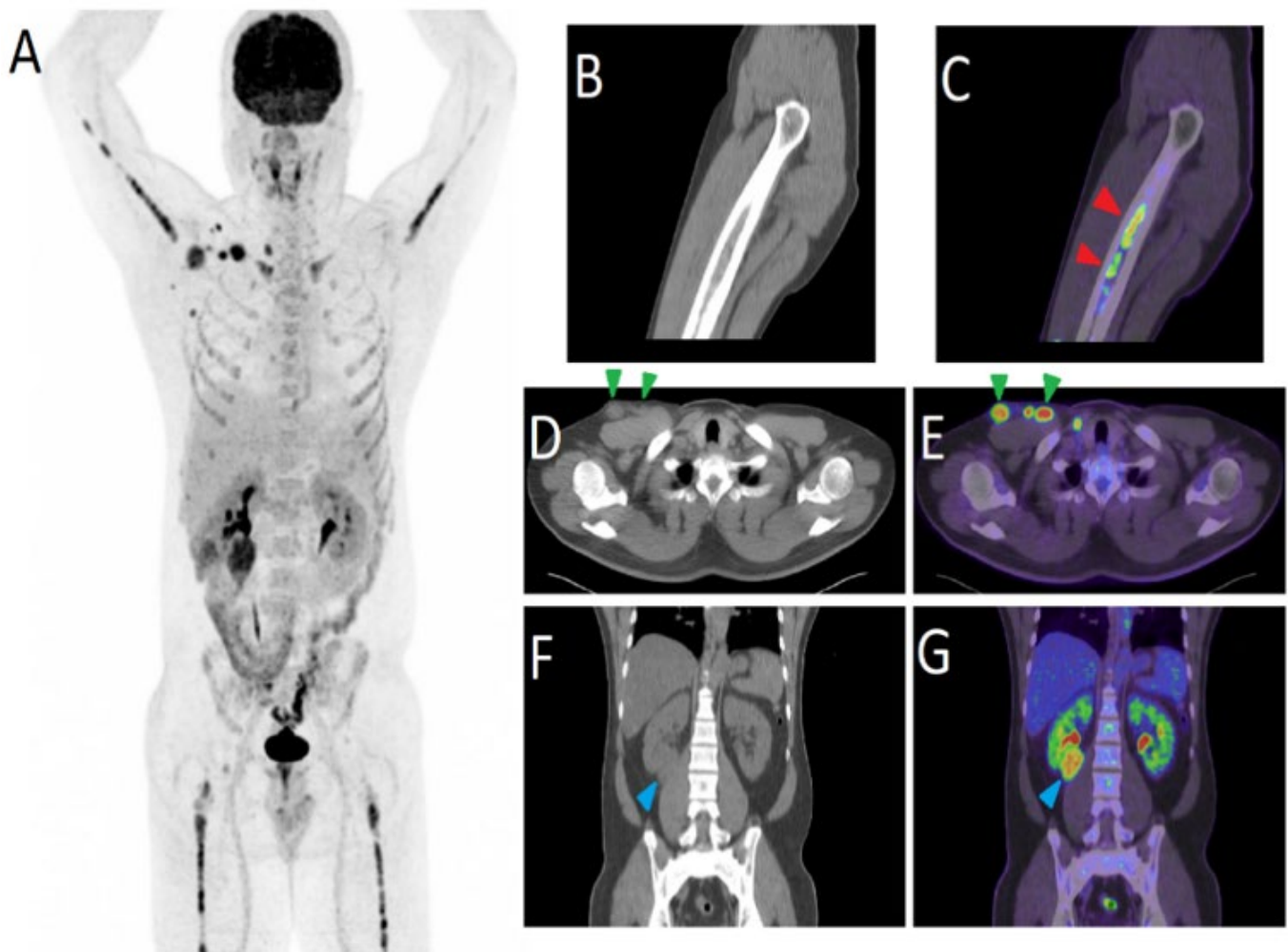


Figure 4. Case (1): FDG PET/CT showing intramedullary and extramedullary involvement: MIP image (A), sagittal CT (B), sagittal fused (C), transaxial CT (D, F) and transaxial fused (E, G) images showing multiple intramedullary lesions in bilateral humerus and femur (red arrowheads), multiple newly developed FDG-avid subcutaneous nodules in the right upper chest wall (green arrowhead) and right lower renal pole lesion (blue arrowhead).

immunostains were positive for CD138, MUM1, CD56, BCL2, c-Myc, P53 with markedly suppressed residual hematopoiesis and increased marrow fibrosis (MF 2). Karyotype was complex: 58~59, XY, +der(1)t(1;17)(p12;q11.1), del(1)(p11p13), +3, +5, +6, +7, +7, +9, +11, +15, -17, +18, +19, +21, +2mar[cp20]/46, XY.¹⁴ Overall findings concluded a diagnosis of plasmablastic transformation of PCM. A new line of therapy, including Elotuzumab–Pomalidomide–dexamethasone, was started, and unfortunately, the patient shortly succumbed.

Case 3. A-63-year-old male with a medical background of diabetes presented in April 2017 with bone pain; imaging revealed multiple bony lytic lesions and pleural-based soft mass (3x1.2cm).

Histopathologic examination of CT-guided biopsy revealed KLC plasmacytoma, BM aspiration showed 3% plasma cells, and the diagnosis of MM was concluded. At presentation, the myeloma cells mostly were mature-looking, and they did not show evidence of aberrant expression of any T-cell associated markers.

Back then, the patient was treated with Bortezomib, Cyclophosphamide, and Dexamethasone chemotherapy combination and achieved complete remission, he underwent stem cell mobilization and harvesting, but he refused stem cell infusion. Thereafter, the patient was kept on lenalidomide maintenance and maintained complete remission. Two years later, the patient presented with biochemical progression with increasing free KLC, and was started on Daratumumab and dexamethasone. A PET/CT scan after 3 months (Figure 5) revealed disease progression with supraclavicular and axillary lymphadenopathy and increased uptake within the muscles. Lymph node (LN) biopsy (Figure 6) revealed an effaced LNs architecture by diffuse sheets of PCs with many plasmablasts, scattered anaplastic forms, and significantly increased mitotic figures. By IHC stains, the neoplastic PCs are positive for CD138, BCL-2, CD10 (weak), CD3 (weak), CD7 (weak), and c-MYC with Kappa restriction.

They are negative for CD45, CD20, PAX 5, CD30, CD4, CD8, CD56, BCL6, cyclin D1, HHV8, CD43, ALK-1 and EBER.

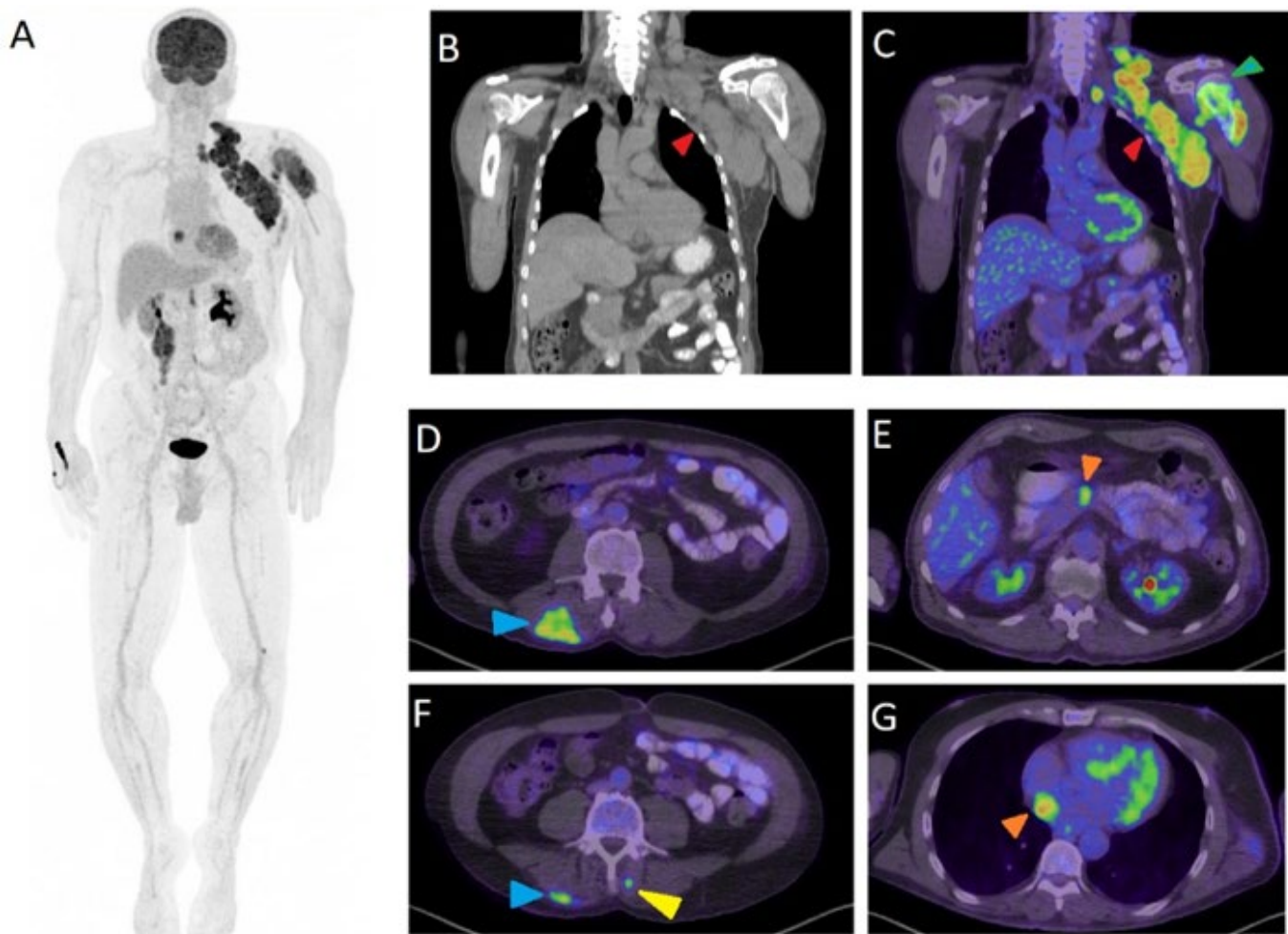


Figure 5. Case (3): FDG PET/CT showing extramedullary involvement: maximum intensity projection (MIP) image (A), coronal CT (B), coronal fused (C) and transaxial fused images (D-G) showing multiple enlarged left axillary and supraclavicular lymph nodes (red arrowheads), left humeral head and neck lesion (green arrowhead), intramuscular involvements (blue arrowheads), FDG-avid peripancreatic lymph node (yellow arrowhead) and paracardiac lymph node (orange arrowhead).

FISH studies on tissue biopsy revealed negativity for BCL-2, BCL-6, and cMYC rearrangements; karyotype was not performed. Carfilzomib was added to Daratumumab and dexamethasone; however, the patient experienced clinical and biochemical progression. Therefore, a new line of chemotherapy [cisplatin, doxorubicin, etoposide, cyclophosphamide] combined with pomalidomide and Carfilzomib was started for two cycles the patient planned for ASCT.

Results of similar cases (Literature review) (Table 1, cases 4-22). Upon an extensive review of English literature, a total of 22 cases of PCNs (including the three cases reported here) showed aberrant co-expression of T-cell associated markers. In addition, 12 out of 17 cases were relapsed PCN while five patients showed an aberrant expression of T-cell associated antigens at their initial presentation.

Among PCN that showed aberrant expression of T-cell associated antigens, 14/16 were male patients and two female patients. The median age of the patients is 57.5 years (range 37-69).

The majority of these patients (10 out of 16 cases)

showed evidence of extramedullary involvement either at presentation or in association with aberrant T-cells markers acquisition; with cutaneous/soft tissue involvement being the most frequently involved extramedullary sites (in five patients) and lymph node involvement in four patients, while four patients had solitary extramedullary plasmacytomas.

Anaplastic/plasmablastic morphology was reported in 11/12. 6/6 cases (including all three cases reported in our center) had a high proliferation index reflected by high KI-67 >60-95% with frequent mitotic figures. EBER/EBV was negative in 12 out of 13 cases

Upon review of the prevalence of T-cell markers expressed on the neoplastic PCs, in the majority of cases (15/22), the clonal PCs showed aberrant expression of CD3 (surface or cytoplasmic at different intensities), 11/22 (50%) showed aberrant expression of CD4. Other T-cell associated markers were rarely reported; CD7 in 3/22 cases, CD2 in 2/22, and CD8 in 1/22 cases. 10/12 cases had poor outcome with very short survival.

Discussion. Aberrant expression of differentiation markers of a different cell lineage on the malignant

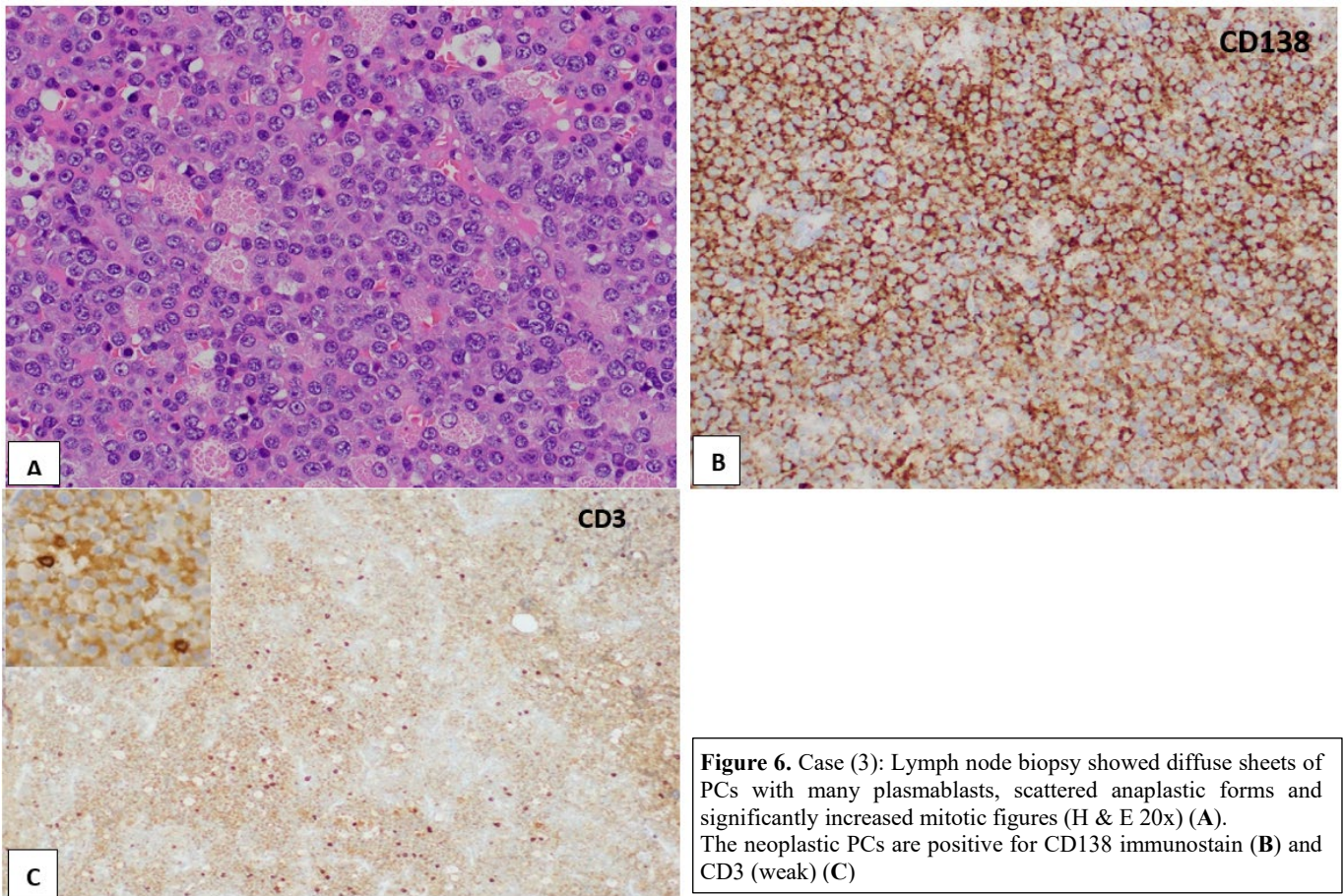


Figure 6. Case (3): Lymph node biopsy showed diffuse sheets of PCs with many plasmablasts, scattered anaplastic forms and significantly increased mitotic figures (H & E 20x) (A). The neoplastic PCs are positive for CD138 immunostain (B) and CD3 (weak) (C)

hematopoietic cells is well documented in the literature. In addition, lineage ambiguity has been recognized in various hematopoietic neoplasms, particularly in those originating from early precursors.²

B-cell neoplasms co-expressing T-cell-associated antigens (other than CD5 or CD43) have been only rarely reported. In addition, aberrant expression of T-cell related markers like CD2, CD3, CD4, CD5, CD7 or CD8 has been rarely documented in chronic lymphocytic leukemia, diffuse large B cell lymphoma, ALK-positive large B cell lymphoma, plasmablastic lymphoma, and Waldenstrom's Macroglobulinemia (WM).³⁻⁸

Most of the reported B-cell neoplasms with aberrant expression of T-cell associated markers were EBV-associated malignancies, including immunodeficiency-associated lymphomas and PBL.⁹

Upregulation of T-cell markers (by gene expression profiling) was detected in a subset of B-cells in patients with WM, suggesting that this small population of cells may have de-differentiated during tumor development.⁸

Comparable to other types of hematologic neoplasms, PCN can show aberrant expression of different lineages' associated antigens with co-expression of B & or myeloid lineage associated antigens being the most commonly reported.¹⁰ Aberrant expression of CD10, CD13, or CD33 on myeloma cells has been associated with poor prognosis.¹¹ CD43 and cytokeratin expression on myeloma cells had been very rarely reported.¹²

Gorczyca and colleagues showed that an aberrant immunophenotype is detected mainly in poorly differentiated or anaplastic myelomas associated with poor prognosis.¹³

Nevertheless, PCNs co-expressing T-cell associated markers are extremely rare, specifically the co-expression of more than one T-cell differentiation marker.

Like PCL, IgD MM often afflicts younger patients than IgG or IgA MM, and often presents as an aggressive disease, with clinical and analytical features associated with bad prognosis (renal failure, thrombocytopenia, elevated LDH, and beta2-microglobulin, abnormal cytogenetics).¹⁰ Lambda-chain preference is also correlated with IgD disease.¹⁰⁻¹²

Among the myeloma cases (151 cases) diagnosed in our center (NCCCR); from 2010 to 2020; we detected three cases of relapsed PCN with aggressive morphologic features (plasmablastic /anaplastic) with extramedullary involvement, high proliferative index ki67 >90%, and all of them showed an aberrant acquisition of T-cell markers with aggressive clinical course. Expression of T-cell associated markers on clonal PCs was confirmed not only by mean of FCM immunophenotyping but also by IHC, with different antibody clones used in each technique (monoclonal antibody UCHT1 mouse monoclonal antibody in FCM) and polyclonal Rabbit Anti-Human CD3 (Dako Omnis)

antibody used by IHC. The T-cell markers were not detected at the initial diagnosis.

The reported cases were detected on a prospective basis, and there was not a comprehensive retrospective screen; therefore, a reliable estimate of prevalence was not postulated.

In the majority of reviewed cases (12/17), the acquisition of T-cell markers occurs mostly during the relapsed status when limited immunophenotypic markers (not usually including T-cell markers) are performed. Hence, the accurate prevalence of aberrant expression of T-cell associated markers in PCN might be underestimated.

The incidence of extramedullary involvement in Multiple Myeloma (MM) was reported between 7-18% at diagnosis and 20% at relapse or progression.¹⁴

In a large series analysis including 1965 patients, Usmani et Al. found that the frequency at diagnosis of extramedullary plasmacytoma (EMP) was 3.4%, with skin and subcutaneous nodules being the most frequently involved sites.¹⁵

The association between immature plasma cell morphology (plasmablastic) and adverse myeloma outcome has been well documented in the literature. Hao et al. recently demonstrated that morphologic features, including plasmablastic morphology, and high mitotic index, significantly correlate with high risk disease [16]. Moreover, anaplastic myeloma variant, in which the malignant PCs are highly pleomorphic, has been reported more common in younger patients with a predisposition for the extramedullary site and poor prognosis.^{14,17} This morphologic variant may present initially at diagnosis¹⁶ or as a feature of disease progression.¹⁸

Aberrant expression of T-cell antigens has also been rarely described in cases with the plasmablastic transformation of PCM, and it has been postulated that

EBV may stimulate T-cell antigen expression in B-lineage neoplasms. However, the majority of cases described in this report were having previously well-established diagnosis of PCN. In addition, the lack of expression of CD30 and EBER/EBV (except in case 1)¹⁹ would argue against the plasmablastic transformation of PCM.

The majority of PCN typically have a low proliferation rate with Ki67 < 10%.²⁰ However, morphologically aggressive PCM with extramedullary involvement has shown a very high Ki67 proliferative index up to 55% to 96% with a strong association with 13q deletion and abnormalities of chromosome 1.²¹

While Spier et Al.⁷ reported no difference in the presenting clinical features, histology, and plasma cell morphology from MM patients who did not express the T-cell antigen; however, the same group reported a very short survival from the demonstration of T-antigens (2-7+ months), with 5/6 (80%) patients died ≤5 months after the study. Similarly, Oliveira et Al.²² suggested that CD3 expression is associated with disease progression and poor prognosis of PCN. Two of three cases detected in our center died within three months of the latest relapse.

Conclusions. Here we discuss an interesting yet rare finding of aberrant acquisition of T-cell associated markers on PCM. This review emphasizes the importance of recognizing atypical and rare immunophenotypic aberrancies in PCN that could lead to diagnostic pitfalls (particularly with extramedullary involvement) and provide important prognostic information.

We conclude that there is an evident association between aberrant expression of T-cell associated markers on PCM and aggressive disease, including plasmablastic morphology, high KI-67, extramedullary involvement, and adverse outcome with short survival.

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