EBMT Registry

# Plasma cell neoplasms (PCN)

## Guide to the completion of the EBMT data collection form: PCD_incl_MM_v2.0

5 June 2024

**EBMT Registry**

EBMT Clinical Research & Registry Department

Co-funded by the European Union

*Co-funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.*

# Table of Contents

# Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on EBMT website.

# Plasma cell neoplasms (PCN)

This form must be completed for all patients whose primary disease for which the HCT/CT treatment is being given is PCN.

PCN are a group of disorders characterised by the abnormal proliferation of plasma cells, which are a type of white blood cell responsible for producing antibodies. Diagnosis of PCN typically involves a combination of blood tests, bone marrow biopsies, imaging studies (such as X-rays or MRIs), and urine tests to detect abnormal proteins produced by the plasma cells.

# Disease

## Date of diagnosis

Report the date of diagnosis. This is often the date on which the bone marrow aspirate and/or biopsy was performed.

## Classification (WHO 2022)

Select the classification of the plasma cell neoplasm according to WHO 2022[1].

### Plasma cell (multiple) myeloma (PCM)

PCM (synonyms: 'Multiple Myeloma (MM)', 'Myeloma', 'myelomatosis') is a malignant lymphoproliferative disorder arising from a clonal plasma cell population. The malignant cells usually produce a monoclonal immunoglobulin readily identifiable in either the plasma (M-component) or the urine (Bence Jones' protein or urinary light chains). The most common clinical presentation in PCM is skeletal damage with lytic bone lesions and generalised osteopenia. Other features include anaemia, hypogammaglobulinemia, renal failure and hypercalcaemia. Indicate the subtype of PCM by checking the corresponding checkbox or select 'Unknown' if this information is not available.

#### *Heavy chain and light chain*

Heavy chain and light chain is the most common PCM subtype in which the malignant plasma cells secrete a complete monoclonal immunoglobulin (M-component) which consists of both a heavy chain

(IgG, IgA, IgD, IgM or IgE) and a light chain (kappa or lambda). The heavy chain is usually either IgG (c.50%) or IgA (c.20%), rarely IgD and very rarely, IgM or IgE.

Please make sure to indicate for this PCM subclassification both the heavy chain type (IgG, IgA, IgD, IgM or IgE) and the light chain type (kappa or lambda).

### *Light chain only*

Light chain only is a PCM subtype where the malignant plasma cells only secrete a light chain component, which can be either kappa or lambda. This constitutes about 20% of all cases of PCM. The light chain can either be detected and quantitated in the serum using the Serum Free Light Chain Assay or in the urine by measuring urinary light chain excretion.

Please make sure to indicate the light chain type (kappa or lambda).

### *Non-secretory*

Non-secretory (synonym: non-producing) is a PCM subtype in which no monoclonal protein is detected in either the serum or the urine. The diagnosis is therefore based on a tissue biopsy, usually the bone marrow. Given the sensitivity of the serum free light chain assay, this is quite rare. Do not classify as non-secretory if the serum free light chain assay has not been performed.

#### *Heavy chain type: IgG-IgA-IgD-IgE-IgM*

Please record the heavy chain type of the M component in the **heavy chain and light chain** type PCM. It should be left blank for light chain PCM and for non-secretory PCM. If the type is unknown, select the corresponding checkbox.

Please note that although there is only one M-component in almost all cases, two (for example, IgG and IgA) may rarely appear simultaneously in the serum/plasma. This is termed biclonal PCM. In these cases, the chain type of the highest value should be selected.

#### *Light chain type: Kappa-Lambda*

Please record the type of light chain (kappa or lambda) for heavy chain and light chain PCM and for light chain only PCM. It should be left blank in non-secretory PCM. If the type is unknown, select the corresponding checkbox.

### Plasma cell leukaemia

Plasma cell leukaemia is a rare and aggressive form of plasma cell neoplasm characterised by the presence of a high number of malignant plasma cells in the blood. This condition is considered a variant of PCM, but it is distinguished by the significant involvement of plasma cells in the peripheral blood.

Symptoms of plasma cell leukaemia may include anaemia, fatigue, bone pain, recurrent infections, and bleeding disorders. Diagnosis typically involves blood tests, bone marrow biopsies, and imaging studies to assess the extent of the disease.

Due to its aggressive nature, plasma cell leukaemia has a poorer prognosis compared to other forms of plasma cell neoplasms.

### Solitary plasmacytoma of bone

Solitary plasmacytoma of bone is a rare type of plasma cell neoplasm that involves the abnormal growth of plasma cells in a single bone or a small group of adjacent bones. Unlike PCM, which affects multiple bones and organs, solitary plasmacytoma of bone is localised and does not involve widespread disease. This condition typically presents as a single bone lesion, most commonly in the spine, pelvis, or ribs. Symptoms may include bone pain, fractures, and swelling at the site of the lesion. Diagnosis of solitary plasmacytoma of bone involves imaging studies such as X-rays, CT scans, or MRIs.

### Immunoglobulin-related (AL) amyloidosis

Immunoglobulin-related (AL) amyloidosis (previously referred to as systemic AL amyloidosis), is a monoclonal plasma cell proliferative disorder. The amyloid protein is derived from abnormal plasma cells that produce monoclonal immunoglobulin light chains, which then form insoluble fibrils that deposit in tissues and disrupt normal function. These amyloid deposits can affect multiple organs, including the heart, kidneys, liver, nerves, and gastrointestinal tract, leading to a wide range of symptoms and complications.

### POEMS (Polyneuropathy, Organomegaly, Endocrinopathy/Edema, Monoclonal-protein, Skin changes)

POEMS syndrome is a rare multisystem disorder that affects multiple organs in the body. The name "POEMS" stands for Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes. This condition is caused by the abnormal growth of plasma cells in the bone marrow, leading to the overproduction of a type of protein called monoclonal gammopathy. The excessive production of this protein can cause a variety of symptoms and complications throughout the body.

Some common symptoms of POEMS syndrome include peripheral neuropathy (nerve damage in the extremities), organomegaly (enlarged organs such as the liver or spleen), endocrine abnormalities (such

as diabetes or thyroid dysfunction), skin changes (such as thickening or darkening of the skin), and the presence of monoclonal gammopathy in the blood.

Diagnosis of POEMS syndrome typically involves a combination of clinical evaluation, blood tests, imaging studies, nerve conduction studies, and bone marrow biopsy to confirm the presence of abnormal plasma cells and monoclonal gammopathy.

| | |
|---|---|
| **Mandatory major criteria** | 1. Polyneuropathy (typically demyelinating)<br>2. Monoclonal plasma cell-proliferative disorder (almost always lambda) |
| **Other major criteria (one required)** | 3. Castleman disease<br>4. Sclerotic bone lesions<br>5. Vascular endothelial growth factor elevation |
| **Minor criteria (one required)** | 6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)<br>7. Extravascular volume overload (edema, pleural effusion, or ascites)<br>8. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)<br>9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails)<br>10. Papilledema<br>11. Thrombocytosis/polycythemia |
| **Other symptoms and signs** | Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhoea, low vitamin B12 values |

Table 1. Diagnostic criteria of POEMS syndrome.

## Monoclonal immunoglobulin deposition disease

Monoclonal immunoglobulin deposition disease (MIDD) is a rare disorder characterised by the abnormal deposition of monoclonal immunoglobulin fragments in various tissues and organs of the body. This condition is closely related to other plasma cell neoplasms, such as PCM and Immunoglobulin-related (AL) amyloidosis, and is often associated with the overproduction of abnormal monoclonal immunoglobulins by plasma cells. The deposited immunoglobulin fragments can accumulate in organs such as the kidneys, heart, liver, and skin, leading to tissue damage and dysfunction.

Symptoms of MIDD can vary depending on the organs affected but may include kidney dysfunction, proteinuria (protein in the urine), edema (swelling), heart failure, liver abnormalities, and skin lesions. Diagnosis of MIDD typically involves a combination of blood tests, urine tests, imaging studies, and tissue biopsies to confirm the presence of monoclonal immunoglobulin deposits and assess organ involvement.

Based on the type of monoclonal immunoglobulin deposits, monoclonal immunoglobulin deposition disease can be classified into three types:

- Light chain deposition disease (LCDD; approximately 80 percent of cases) – Deposits are composed of light chains only. In approximately 80 to 90 percent of LCDD, the light chains are kappa light chains.
- Heavy chain deposition disease (HCDD; approximately 10 percent of cases) – Deposits are composed of heavy chains only.
- Light and heavy chain deposition disease (LHCDD; approximately 10 percent of cases) – Deposits are composed of both light and heavy chains.

### Other

If the classification of plasma cell disorder is not listed, check the box “Other” and specify it (e.g. Nemalinic myopathy should be registered under “Other”).

Note: rarely, plasmacytomas can occur on different sites simultaneously. This would be called “multiple plasmacytomas”. Bone marrow infiltration must be excluded.

Below is a table to help with the registration of the PCN diagnosis if multiple PCN have been diagnosed in the patient history:

| | |
|---|---|
| **Main diagnosis is PCM, this is the usual indication for HCT** | |
| **Plasmacytoma**: | |
| Precedes the PCM diagnosis | The plasmacytoma is not considered the indication for the HCT and we do not require that it be registered |
| **POEMS**: | |
| Simultaneous to the PCM diagnosis | This would be considered as POEMS, and POEMS should be registered as indication for HCT |

| | |
|---|---|
| After HCT for PCM | POEMS, to be registered as secondary malignancy |
| **Monoclonal immunoglobulin deposition disease**: | |
| Precedes the PCM diagnosis<br><br>Simultaneous to the PCM diagnosis | Monoclonal immunoglobulin deposition disease is considered as a diagnosis on its own. However, if it is not considered to be an indication for HCT, it does not need to be registered.<br><br>If Monoclonal immunoglobulin deposition disease is considered to also be an indication for HCT, then both diagnoses should be registered as main. |
| After HCT for PCM | Monoclonal immunoglobulin deposition disease, to be registered as secondary malignancy |
| **Immunoglobulin-related (AL) amyloidosis**: | |
| Precedes the PCM diagnosis<br>Simultaneous to the PCM diagnosis | If the patient has both diagnoses, then the indication for HCT is PCM. |
| After HCT for PCM | Immunoglobulin-related (AL) amyloidosis to be registered as a secondary diagnosis |

Table 2. Classification of Plasma Cell Neoplasms (PCN).

# Staging (PCM only)

## Staging at diagnosis

### Revised ISS

Indicate Revised ISS stage (R-ISS) according to the parameters listed in table 3.

| **Revised ISS definitions** | |
|---|---|
| **Stage** | **Definition** |
| I | I: ISS I without high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and |

| | |
|---|---|
| | normal LDH |
| II | II: not R-ISS I or III |
| III | III: ISS III with high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and/or high LDH |
| Unknown | The R-ISS stage is not known. |

Table 3. Definitions of Revised ISS stages.

### ISS

Indicate ISS stage[2] according to the parameters listed in table 4.

| **ISS definitions** | |
|---|---|
| **Stage** | **Definition** |
| I | B2-µglob (mg/L) <3.5 and albumin (g/L) >35 |
| II | B2-µglob (mg/L) <3.5 and albumin (g/L) <35<br>**or** B2-µglob (mg/:L) 3.5 ≤ 5.5 and any albumin level |
| III | B2-µglob (mg/L) >5.5 and any albumin level |
| Unknown | The ISS stage is not known. |

Table 4. Definitions of ISS stages.

## Extramedullary disease (EMD)

EMD is an aggressive form of PCM, characterised by the ability of a clone and/or subclone to thrive and grow independently of the bone marrow microenvironment.

Please indicate if extramedullary involvement was diagnosed or not, or mark as unknown by ticking the corresponding box.

If EMD was diagnosed, please fill out the corresponding sub questions and indicate the method of diagnosis, the location of EMD, the number of sites, and specify the organs involved.

# Chromosome analysis

## Not applicable for Immunoglobulin-related (AL) amyloidosis

### Chromosome analysis done at diagnosis

In this section, describe the results of the chromosome analysis (all methods including FISH) for all PCN diagnoses except Immunoglobulin-related (AL) amyloidosis.

Indicate if chromosome analysis was done or not at time of diagnosis. Check **Unknown** if it is not known whether it was performed.

Note: Chromosome analysis is very important since specific abnormalities have emerged as one of the major prognostic factors. Please complete this section as carefully as possible in each single patient.

### What were the results?

**Normal** - the chromosome analysis has been performed and the results have been found normal

**Abnormal** - the chromosome analysis has been performed and abnormalities have been found. In addition, indicate the total number of different abnormalities present (**number of abnormalities present**).

**Failed** - the chromosome analysis was done but failed

Note: **'Normal' is generally not an answer option** for this question, because that would imply that the test was not performed on bone marrow plasma cells.

### Date of chromosome analysis

Indicate the date of the chromosome analysis. Select **Unknown** if the date is unavailable.

### Chromosome analysis method

Indicate the method used for chromosome analysis. Abnormalities can be detected by all methods, though it is almost always by FISH for PCN.

### Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent, Present** or **Not evaluated**.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality, marking whether it was **Absent** or **Present.**

## Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results as per the abnormalities table please enter the complete karyotype. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra, missing or mutated autosomal chromosomes. For example, **47, XY, +18** indicates that the patient has 47 chromosomes, is a male, and has an additional copy of autosomal chromosome 18.

# Bibliography

1. Alaggio, R., Amador, C., Anagnostopoulos, I. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 36, 1720–1748 (2022). https://doi.org/10.1038/s41375-022-01620-2

2. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep 10;33(26):2863-9. doi: 10.1200/JCO.2015.61.2267. Epub 2015 Aug 3. PMID: 26240224; PMCID: PMC4846284.