Plasma cell disorders (PCD) incl. multiple myeloma (MM)

Guide to the completion of the EBMT data collection form: PCD_incl_MM_v1.0

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EBMT Registry

EBMT Clinical Research & Registry Department

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Plasma cell disorders (including multiple myeloma)

Apart from plasma cell myeloma, the plasma cell disorders group includes the following conditions (1):

Plasma cell leukaemia

Solitary Plasmacytoma

      Solitary plasmacytoma of bone

      Solitary plasmacytoma with minimal marrow involvement

      Extraosseous plasmacytoma

Monoclonal immunoglobulin deposition diseases

      Primary Amyloidosis

      Light chain and Heavy chain deposition diseases

POEMS syndrome

1. Date of diagnosis

Report the date of diagnosis if this was the indication for a treatment. This is often the date on which the bone marrow aspirate and/or biopsy was performed.

2. PCD incl. MM Classification

Select the classification of the plasma cell disorder and check the box next to it.

2.1. Multiple myeloma

(MM; synonyms: '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 MM is skeletal damage with lytic bone lesions and generalised osteopenia. Other features include anaemia, hypogammaglobulinemia, renal failure and hypercalcaemia. Indicate the subtype of multiple myeloma by checking the corresponding checkbox or select 'Unknown' if this information is not available.

2.1.1. MM (heavy chain and light chain)

is the most common myeloma 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 myeloma subclassification both the heavy chain type (IgG, IgA, IgD, IgM or IgE) and the light chain type (kappa or lambda).

2.1.2. MM light chain

is a myeloma subtype where the malignant plasma cells only secrete a light chain component, which can only be either kappa or lambda. This constitutes about 20% of all cases of myeloma. 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. When entering the classification, please record it as the light chain type.

2.1.3. MM non-secretory

(synonym: non-producing) is a myeloma 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.

2.1.4. Heavy chain type: IgG-IgA-IgD-IgE-IgM

Please record the heavy chain type of the M component (= monoclonal protein = monoclonal immunoglobulin = monoclonal Ig) in the **heavy chain and light chain** type myeloma. It should be left blank for light chain myeloma and for non-secretory myeloma. 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 myeloma. In these cases, the chain type of the highest value should be entered into the database.

Please record the type of light chain (kappa or lambda) of the M-component (e.g. IgG kappa, IgG lambda) in light chain myeloma as well as in heavy chain and light chain type myeloma or the type of light chain in either the serum or the urine in light chain myeloma. It should be left blank in non-secretory MM. If the type is unknown, select the corresponding checkbox.

2.2. Plasma cell leukaemia

This is a rare aggressive plasma cell disease which is generally treated like myeloma.

2.3. Solitary plasmacytoma (SP)

This is a biopsy-proven solitary plasma cell tumour in the bone or soft tissue with evidence of clonal plasma cells. The bone marrow is normal with no evidence of clonal plasma cells. The skeletal survey and MRI (or CT) of spine and pelvis are normal except for the primary lesion. The risk of progression to myeloma is about 10% over the following three years.

Solitary plasmacytoma (SP) with minimal marrow involvement: This is a biopsy-proven solitary plasma cell tumour in the bone or soft tissue with evidence of clonal plasma cells. There are clonal plasma cells within the bone marrow which constitute less than 10% of bone marrow cellularity. The skeletal survey and MRI (or CT) of spine and pelvis are normal except for the primary lesion. The risk of progression to myeloma is about 60% (bone) or 20% (soft tissue) within three years.

2.4. Systemic AL Amyloidosis

This is characterised by the presence of an amyloid-related systemic syndrome e.g. renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement and positive staining for Amyloid by Congo red in any tissue e.g. fat aspirate, bone marrow, or organ biopsy.

As both wild-type and mutant ATTR amyloidosis, other distinct non-clonal forms of amyloidosis, are now diagnosed more frequently, the diagnosis of light chain amyloidosis requires that the Amyloid deposit be shown to be light-chain-related by direct examination by either immunohistochemical staining of the amyloid deposits using monospecific antibodies, mass spectrometry-based proteomic analysis, or immunoelectron microscopy.

Other evidence of a monoclonal plasma cell proliferative disorder includes the presence of a serum or urine monoclonal protein, an abnormal free light-chain ratio, or clonal plasma cells in the bone marrow.

2.5. Monoclonal light and heavy chain deposition disease (LCDD, LHCDD and HCDD)

A rare non-amyloid monoclonal immunoglobulin deposition disease characterized by secretion of abnormal light and heavy chains, which are deposited in tissues and cause organ dysfunction, but do not form amyloid beta-pleated sheets or produce an amyloid P component. The condition most frequently occurs in association with multiple myeloma. The kidneys are most commonly affected (clinically manifesting as nephrotic syndrome and renal failure), but liver, heart, peripheral nerves, blood vessels, and joints may also be involved.

2.6. POEMS

(Polyneuropathy, Organomegaly, Endocrinopathy/edema, Monoclonal-protein, Skin changes): POEMS can affect multiple systems in the body. It is characterised by the following features:

Polyneuropathy

Monoclonal plasma cell proliferative disorder (almost always λ)

Any one of the following three other major criteria:

> Sclerotic bone lesions
>
> Castleman's disease
>
> Elevated levels of VEGF

Any one of the following six minor criteria:

> Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
>
> Extravascular volume overload (oedema, pleural effusion, or ascites)
>
> Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
>
> Skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails)
>
> Papilloedema
>
> Thrombocytosis/polycythaemia

2.7. 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 PCD diagnosis if multiple PCD have been diagnosed in the patient history:

Main diagnosis is Multiple Myeloma (MM), this is the usual indication for transplant	
Plasmacytoma:	
Precedes the MM diagnosis	The plasmacytoma is not considered the indication for the transplant and we do not require that it be registered
POEMS:	
Simultaneous to the MM diagnosis	This would be considered as POEMS, and POEMS should be registered as indication for transplant
After transplant for MM	POEMS, to be registered as secondary malignancy
Monoclonal light and heavy chain deposition disease (LCDD/HCDD):	
Precedes the MM diagnosis	LCDD/HCDD is considered as a diagnosis on its own. However, if it is not considered to be indication for transplant, it does not need to be registered.
Simultaneous to the MM diagnosis	If LCDD/HCDD is considered to also be indication for transplant, then both diagnoses should be registered as main.
After transplant for MM	LCDD/HCDD, to be registered as secondary malignancy
Amyloidosis:	
Precedes the MM diagnosis	If the patient has both diagnoses, then the indication for

Simultaneous to the MM diagnosis	transplant is Myeloma.
After transplant for MM	Amyloidosis to be registered as a secondary diagnosis

Table 1, Classification of Plasma Cell Disorders (PCD) including Multiple Myeloma (MM).

3. Staging at diagnosis (report for Multiple myeloma only)

Indicate ISS stage and Revised ISS (R-ISS) stage according to the parameters listed in tables # and #. Staging is the clinical classification of the extent of disease at diagnosis.

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 **or** B2-µglob (mg/:L) 3.5 ≤ 5.5
III	B2-µglob (mg/:L) >5.5
Unknown	The ISS stage is not known.

Table 2, definitions of ISS stages.

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: any ISS 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.

4. Extramedullary disease (EMD) (report for Multiple myeloma only)

EMD is an aggressive form of multiple myeloma (MM), 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.

4.1. Indicate if EMD was diagnosed on MRI or not, or if it is unknown.

4.2. Indicate if EMD was diagnosed on PET-CT or not, or if it is unknown.

4.3. Specify the location of EMD by marking it as paraskeletal, organ (i.e. extramedullary), or both (paraskeletal AND organ (extramedullary)) or as unknown, if the location is not known.

4.4. Indicate the number of sites or mark as unknown.

4.5. Specify the organ or organs where EMD was found.

5. Chromosome analysis at diagnosis (report for all types except Systemic AL Amyloidosis)

Choose the answer based on all analyses from diagnosis, but before treatment. Please enter the results of the most recent complete analysis. Abnormalities to be reported can be detected by all methods, though it is almost always by FISH:

Not done or failed - choose this answer option if chromosome analysis was not done before treatment or if it failed

Abnormal - choose this answer option if at least one analysis has been found to be abnormal. Write the number of abnormalities present in the most recent analysis with abnormal results

Unknown - if it is unknown whether chromosome analysis was performed before treatment was started

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. If this is the case and the result is shown as normal in the patient record, it should be reported here as **Not done/failed**.

5.1. Date of chromosome analysis (if tested)

Indicate the date of the most recent, complete chromosome analysis.

If chromosome analysis was not done, failed or unknown, leave the field blank.

5.2. Chromosome analysis method

Indicate the method used for chromosome analysis. In PCD, it is almost always FISH.

If chromosome analysis was not done, failed or unknown, leave the field blank.

5.3. Chromosome analysis details

Indicate per each abnormality in the table if it was absent, present, or not evaluated in the chromosome analysis reported above. If there were other abnormalities tested that are not mentioned in the table, specify the abnormality and if it was absent or present.

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.

5.4. Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results based on the abnormalities listed in the Table, or if the result of the chromosome analysis is too complex, the complete karyotype should be entered here. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing 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. Campo E, Harris NL, Pileri SA, Jaffe ES, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Who Classification of Tum; 2017. 586 p.