UP–DATE ON SOLITARY PLASMACYTOMA AND ITS MAIN DIFFERENCES WITH MULTIPLE MYELOMA

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Solitary plasmacytoma is plasma cell neoplasm. It is a localized bone disease and for this reason it is different from multiple myeloma (systemic plasma cell neoplasm). Sometimes, solitary plasmacytoma precedes a following multiple myeloma. Clinical findings of solitary plasmacytoma are related to the univocal localization on damaged bone, while laboratory findings could be similar to multiple myeloma (i.e. M component, kidney dysfunction, blood calcium alterations, increased β2-microglobulin). However, during a solitary plasmacytoma, laboratory findings could not be present contemporaneously such clinical complications (i.e. kidney failure, immunological disorders with a trend toward infectious disease and/or autoimmunity, neurological disorders, haematological disorders, amyloidosis, POEMS syndrome). These raise the reason because solitary plasmacytoma has better prognosis compared to multiple myeloma.

Key Words: solitary plasmacytoma, multiple myeloma.

General information
Plasmacytoma, a clonal neoplastic disorder of bone marrow that originates from plasma cells, the last maturation stage of B lymphocytes [1–2], may appear as three different diseases: multiple myeloma (systemic disease), extramedullary plasmacytoma and solitary plasmacytoma (localized bone disease) [3]. Solitary plasmacytoma may be an isolated disease or the first manifestation of a following multiple myeloma [4]. The isolated form of plasmacytoma seems to have a better prognosis [4, 5], while in case of subsequent multiple myeloma the prognosis is different [6]. Usually, clonal plasma cells involved in plasmacytoma produce a monoclonal immunoglobulin as well as κ and λ light chains [7, 8]. A quantitative assay of plasma monoclonal immunoglobulin may be performed during a plasmacytoma and may also reflect tumor growth [9]. Commonly this described alteration may appear as monoclonal spike in γ area, β area or rarely in α2 area on serum electrophoresis [10]. In case of light chain production patient’s immunoelectrophoresis in serum and urine might reveal the clonal activity [8].

During solitary plasmacytoma, plasma cells monoclonal proliferation is localized in bone marrow, bone pain, bone destruction and pathological fractures represent the most common clinical sign of the disease [3, 5]. Moreover, bone damages may also be responsible for alteration of blood calcium levels [3], but this alteration is more frequent in multiple myeloma than in solitary plasmacytoma.

Clinical complications during plasma cells disorders are related also to immunoglobulin production which is responsible for a relative immunodeficiency (specific antigen immune response seems to be reduced during plasmacytoma) and kidney damages [1, 3, 9]. Kidney damages are principally related to light chains and are quickly eliminated representing the Beence–Jones protein in the urine [9, 10]. Moreover, immunoglobulin produced by plasmacytoma may be insoluble if cold temperature is present, so causing a cryoglobulinemia [5, 11], in particular if a chronic C viral hepatitis is associated [5, 12]; kidney failure may result from reduced immunoglobulin elimination in the urine [9]. Amyloidosis may also be a consequence of light chains production by plasmacytoma [13].

Rarely we may observe a non–secretory plasmacytoma [14], in which κ and λ chains are intracytoplasmic and may be detected by immunofluorescence [15].

New insights on aetiology
The aetiology of plasmacytoma is still unknown and although different pathways and stimuli seem to be involved. Recently several hypothesis has been underlined, including a possible role of viral infection [5, 9]. A viral chronic, clinical or subclinical infection, in fact, has been often researched to understand its possible role as oncological risk factor in newly induced lymphoproliferative disease other than cytogenetics (e.g. deletion of chromosome 13q) [16]. In particular, hepatitis C virus has been often suggested to play a role in pathophysiology of lymphoproliferative malignancies [17–20]. High HCV seroprevalence, in fact, was revealed in patients affected by B–cell non–Hodgkin’s lymphoma [20, 21]; these data has been also confirmed by the presence of HCV in bone marrow [22]. Moreover, HCV seroprevalence has been also identified in bone marrow of patients affected by multiple myeloma so underlying one more time the role of HCV infection as risk factor for development of several haematological malignancies [23]. Lymphotropic action of HCV is related to its binding on protein expressed on lymphocyte surface, named CD 81 [20, 24]. However, further study should confirm epidemiological data because HCV seroprevalence seems to be higher in some countries than others [25].
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that systemic complications may be present also in 

radiographic lesions and bone fractures [5, 9]. Howev-

er, examination showing joint alteration and/or well defined 

bone pain and bone alterations confirmed by X-ray 

examination. Usually, solitary plasmacytoma is not related to a 

specific clinical evaluation. Bone marrow aspirate and/or bone marrow biopsy 

are normal in solitary plasmacytoma, while are usually 
diagnostic in multiple myeloma (presence of more than 

15% of neoplastic plasma cells) [9]; only localised bone 

biopsy directed to damaged bone allows to identify 

neoplastic plasma cells and so a solitary plasmacyto-

ma. Usually, solitary plasmacytoma is not related to a 
detectable M-component in serum electrophoresis, 

while light chains could be produced [5]. Intracytoplas-

matic monoclonal immunoglobulin production could be 

found in non-secretory plasmacytoma [14, 15].

Extramedullary solitary plasmacytoma is very rare 

and diagnosis could be checked out only with a locali-

zed biopsy. Usually, we may have a solitary extrame-

dullary plasmacytoma localized on nasopharynx, na-

sal and gastrointestinal mucosa [28, 29], but also other 

unusual sites are reported [30, 31].

However, we report below the most common clini-

cal signs and symptoms associated to plasma cells 
malignancy; it is also important underline that during a 

solitary plasmacytoma only few of the following mani-

festations may be present and solitary plasmacytoma 
diagnosis is often related only to a specific clinical eval-

uation of a bone related symptom.

**General clinical data**

Plasma cells neoplasm usually affects people in the 

range of 50–80 years [5]. Relevant clinical signs of soli-
dary plasmacytoma may be summarised in localised 
bone pain and bone alterations confirmed by X-ray 

examination showing joint alteration and/or well defined 

radiographic lesions and bone fractures [5, 9]. Howev-

er, other clinical data may be referred and are related to 

the three pathophysiological mechanisms of the dis-

ease: localised bone symptoms, M-component, alter-

ations in blood calcium levels. These findings confirm 

that systemic complications may be present also in 

solitary plasmacytoma, not only in multiple myeloma. 

So, complications may be represented also by neuro-

logical, immunological, haematological, infectious, 
nephrological findings.

**Bone metabolism and pathological findings.** Bone 

lysis and/or bone fractures are responsible for locali-

zed pain of patients affected by solitary plasmacyto-

ma. Bone pain, in fact, is the most common clinical 
symptom of patients affected by plasma cells mali-

gnancy. Bone pain is prevalent during movements, while 

is infrequent during the night, like in bone metastatic 
carcinoma. Bone lesions are induced by neoplastic cells 
in bone marrow (i.e. neoplastic plasma cells) which re-

lease osteoclast activating factor, so inducing osteo-

clasts activation. Osteoclasts activity destroys the bone 

structure and it seems not opposed by new bone for-
mation by osteoblasts. Glucocorticoids administration 

may stop this bone management (osteoclasts/osteoblasts imbalance) because it is due to cytokines re-

lease by neoplastic plasma cells.

In fact, an increase in vascular endothelial growth fac-
tor (VEGF), transforming growth factor beta 1 (TGFβ–1) 

and interleukin 6 (IL–6) levels have been found in patients 

affected by lymphoproliferative disorders [32, 33].

Yet, increased levels of endostatin has also been 

found in active phases of multiple myeloma, but its role 

should be further investigated in solitary plasmacyto-

ma [34].

Furthermore, also osteopontin (OPN), an adhesive 
glycophosphoprotein produced by several cell types 

seem to be involved in plasmacytoma [35, 36]. Although 

OPN is produced by both osteoclasts and osteoblasts 

it seems to play an important role on mechanical bone 
remodelling in several conditions like accelerated bone 

loss conditions such as myeloma and bone metastasis 

[35–37]. Serum OPN seems also to have a correlation 

with β–2–microglobulin levels, while there is no corre-

lation with serum OPN levels and severity of bone mor-

bidity [36].

Localised bone lesions may expand to the original 

point and may lead to compression signs, in particular 

if vertebrae are involved (e.g. spinal cord compression).

This is a really interesting aspect of patients affected 

by plasma cell disorders because, associated to sep-

sis, bone damages and related symptoms may repre-

sent a common cause of medical emergencies. Fur-

thermore, bone lysis, also if localised, may result in 
calcium mobilisation from bone so leading sometimes to 

hypercalcemia.

**Hypercalcemia.** Hypercalcemia is related to calci-
um mobilisation from affected bone and may lead to 

acute and/or chronic complications. Hypercalcemia, in 

fact, is related only to bone damage related to osteo-
clast/osteoblast impaired activity and to pathological 

fractures, while parathormone and vitamin D3 seem not 
to be involved. Acute complications are principally re-

presented by neurological disturbances such as lethar-

gy, weakness, depression and confusion, while chronic 
effects of hypercalcemia are related to kidney dam-

ages. However, hypercalcemia is rare in case of solitary 

plasmacytoma, while it is more frequent in case of 

multiple myeloma.

**Laboratory and instrumental data on solitary 

plasmacytoma**

Laboratory signs of solitary plasmacytoma are usu-

ally related to the immunoglobulin production, if secre-
tory component is present (i.e. monoclonal gammopa-

thy in serum electrophoresis, light chains production 
detectable in serum and/or urine, cryoglobulinaemia), 

blood calcium alterations, kidney dysfunction and se-

rum β–2–microglobulin levels [1, 9]. Moreover, β–2–mi-

croglobulin has also a relevant role in staging and prog-

dnosis of multiple myeloma [9].

Amyloidosis [13] and polyneuropathy, organomega-

ly, endocrinopathy, multiple myeloma and skin changes 

(POEMS syndrome) [26] may also be associated as 

complication of a secretory plasmacytoma. Usually pre-

ferred bone localisations of solitary plasmacytoma are 

sternum, skull, rib, jaw, humerus, femur, pelvis and in 

these cases radiographic images show an unique coin 

lesion without peripheral edema, in particular if comput-
ed tomography is performed [9, 27]. However, in rare 
cases also diffuse bone alterations are reported.

Bone marrow aspirate and/or bone marrow biopsy 

are normal in solitary plasmacytoma, while are usually 
diagnostic in multiple myeloma (presence of more than 

15% of neoplastic plasma cells) [9]; only localised bone 

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found in non-secretory plasmacytoma [14, 15].

Osteopontin (OPN), an adhesive glycoprotein produced 

by several cell types seems to be involved in plasmacytoma 

[35, 36]. Although OPN is produced by both osteoclasts 

and osteoblasts it seems to play an important role on 

mechanical bone remodelling in several conditions like 

accelerated bone loss conditions such as myeloma and 

bone metastasis [35–37]. Serum OPN seems also to 

have a correlation with β–2–microglobulin levels, while 

there is no correlation with serum OPN levels and severity of bone morbidity [36].

Localised bone lesions may expand to the original point and may lead to compression signs, in particular if vertebrae are involved (e.g. spinal cord compression). This is a really interesting aspect of patients affected by plasma cell disorders because, associated to sepsis, bone damages and related symptoms may represent a common cause of medical emergencies. Furthermore, bone lysis, also if localised, may result in calcium mobilisation from bone so leading sometimes to hypercalcemia.
**Kidney failure.** Hypercalcemia contributes to kidney failure of patients affected by plasma cells disorders, in particular if M-component (toxic effects of light chain production) and amyloidosis are also present. Hypercalcemia often leads to tubular damages such as Fanconi syndrome characterised by glucose and amino-acids loss in the urine, defects to acidify urine and proteinuria. Proteinuria is related to the excess of light chains fallen on tubules, while it is a nonselective proteinuria if glomeruli are involved. Yet, glomerular deposit of amyloid, recurrent infections in the urinary tract and filtration troubles related to the presence of light chains are other factors inducing progressive kidney failure. Increase in light chains production present in tubules leads to an overload resulting in the toxic nephrological effects of light chain production of patients affected by plasmacytoma.

**Infectious disease and sepsis.** Infections are common in patients affected by plasma cells disorders, in particular if M-component is present. If we could exclude M-component we probably find a hypogammaglobulinemia related to destruction/fall of normal antibodies and to a down regulation of immunoglobulin production by non-neoplastic plasma cells. This action is probably exerted by a small population of regulatory cells. Moreover, the reduced immunoglobulin production of patients affected by plasmacytoma associated to M-component has been also associated to a poor antibodies response to polysaccharide [9]. For this reason we may have a susceptibility to infections in these patients and pneumonia and pyelonephritis are the most common type of infections described. Several bacterial pathogens, grampositive and gramnegative, are involved in these cases and are responsible of recurrent pyelonephritis of patients affected by plasmacytoma. Yet, recurrent pyelonephritis seem to be also responsible of progressive kidney dysfunction. Furthermore, serious infection, if not well treated and/or if a timely diagnosis has not been done could also lead to a sepsis and sepsis has been identified as one of the most common cause of death of these patients being often associated to the occurrence of disseminated intravascular coagulation (DIC) and then to septic shock [38, 39].

Moreover, produced immunoglobulin may also have a trend to fall at cold temperature so inducing a cryoglobulinemia [5, 11], in particular if a chronic HCV infection is present. Patients affected by cryoglobulinaemia often show also a rheumatoid factor positivity that may be present as subclinical and asymptomatic positivity or may be responsible of clinical arthritis with joints’ involvement [40].

**Neurological disorders.** Neurological symptoms rarely occur in solitary plasmacytoma patients and could be related to several alterations found in myeloma pathology. We have already underlined the role of hypercalcemia inducing clinical neurological disorders such as lethargy, weakness, confusion and strong depression.

Yet, neurological symptoms could also be due to hyperviscosity. Hyperviscosity is defined on the basis of serum viscosity compared to water and is related primary to the excess of paraprotein (i.e. principally immunoglobulin) production by neoplastic plasma cells such as full immunoglobulin or light chains. Hyperviscosity related symptoms could be summarised in headache, visual disturbances, astenia, rethiopathy, sensorial peripheral neuropathy and mental confusion.

On the other hand also peripheral neurological disorders may be present in patients with plasma cells disorders both to sensorial or motor function such as spinal cord compression, radicular pain due to bone lesion expansion and its peripheral oedema and also loss of bowel or bladder control. Yet, sensorial peripheral nerves damages could be related to amyloid infiltration inducing different types of sensorial mono-poly-neuropathy. Rarely we may have a peripheral nerves ischemia due to autoimmune mechanism.

**Haematological disorders.** Anemia is rarely present in solitary plasmacytoma because the disease dominantly occurs in an isolated bone and does not involve the full bone marrow, so hematopoesis has not been hostile. However, when present, anemia is probably related to hemolysis due to the excess of produced paraproteins. Granulocytopenia and thrombocytopenia are very rare and usually due to autoimmune mechanisms.

On the other hand, molecular abnormalities may be present on clotting activity. Haemorragic trends could be observed if M-component binds clotting factors such as clotting factor I, clotting factor II, clotting factor V, clotting factor VII, clotting factor VIII or von Willenbrand factor, so inducing an acquired disorders mimicking inherited deficiency. Laboratory findings may confirm this acquired disorders with different tests focused to identify quantitation of clotting factors and after to its related impaired activity (adhesion molecules, aggregation defects, impaired thrombin/fibrin formation, prolonged prothrombin time, prolonged activated partial thromboplastin time) [9].

Thrombotic trends may also be observed in patients affected by plasma cells disorders and could be related firstly to the acquired thrombophilia present in malignancy which could have several mechanisms [41, 42]. Yet, also anticardiolipin antibodies and/or lupus anticoagulant could be produced by neoplastic plasma cells inducing a secondary antiphospholipids syndrome.

**Other.** The reason is unknown because plasma cell proliferation in plasma cells tumor is located dominantly in bone marrow, while rarely involves lymphatic tissues such as lymph nodes, spleen and intestinal lymphatic zone, so lymphatic tissue involvement in solitary plasmacytoma is very rare, but we may find it during complication such as amyloidosis and/or POEMS syndrome.

**Amyloidosis.** Amyloidosis is a disease characterised by extracellular deposition of a well identified protein (i.e. amyloid). Amyloid deposition may occur in several tissues and/or organs and may induce specific and progressive organ dysfunction [43]. Also different forms of amyloid have been reported and among them we may identify also a light chain (κ or λ) or β2–microglobulinemia prevalence in its structure [44, 45]. Of
course, we have previously underlined the role of both components (i.e. light chains and $\beta$-2-microglobuline-mia) in pathophysiology of plasma cells neoplasms, so we may have amyloidosis as complication of such case of plasmacytoma. Usually, in the daily clinical management we may observe two different form of amyloidosis during plasmacytoma: localised amyloidosis, in which only one or few tissues are damaged by amyloid protein, and systemic amyloidosis in which we may identify amyloid protein in several tissues. However, systemic amyloidosis commonly possesses an inherited ground [46]. During amyloidosis we may observe cardiac damages (perycarditis, dilatative cardiomyopathy, heath failure), liver disease (persistent aminotransferase elevation, hepatomegaly, liver fibrosis, portal hypertension), skin alterations with several clinical manifestations, acquired clotting deficiencies with a trend to hemorrhagic disorders, endocrinological disorders (several type of thyroid dysfunction, thyroid cancer, chronic pancreatic illness), chronic arthritis, central and peripheral neuropathy, gastroenterological disorders (maccroglossia, intraoral soft tissue masses on the oral mucosa [47]), pancreatic disfunction, bowel localized disfunction, nephrological disorders (in particular nephrotic syndrome) and rarely temporal giant cells arteritis [48, 49]. Because both $\beta$-2-microglobulinenia and light chains are produced during plasmacytoma's natural history, reduction of their levels by plasmacytoma therapy (chemotherapy and/or radiotherapy) may improve progression and outcome of amyloidosis. In particular, a recent case report underlined a possible therapeutic support of chemotherapy in primary amyloidosis [50].

POEMS. The findings of POEMS syndrome are related to a progressive peripheral neuropathological disorder inducing continuous pain. However, POEMS represents only a small subset of total peripheral neuropathy present in plasmacytoma, so it is very rare a POEMS diagnosis, in particular during a solitary plasmacytoma. Unlike, in typical plasmacytoma patients affected by POEMS syndrome show frequently lymphatic tissues involvement such as lymph nodes swelling, hepatomegaly and splenomegaly. However, also cardiomegaly has been shown in POEMS syndrome. Several endocrinopathy have been described in these patients and diabetes (described as type 2 diabetes) is frequent as thyroid disfunction, in particular secondary hypothyroidism following an autoimmune thyroid disease. Adrenal insufficiency is rarely noted, while hyperprolactinemia has been often described and it is secondary to the loss of hypothalamus inhibitory control. Furthermore, amenorrea could be presented in males such as impotence and gynecomastia in females. It seems that plasmacytoma treatment could improve POEMS syndrome manifestations [51].

Natural history

We previously underlined that the majority of patients affected by solitary plasmacytoma have an indolent course, so showing a really slow progression of the disease over many years. Usually, in fact, patients have a solitary plasmacytoma diagnosis after evaluation of progressive bone pain or after well identified M-component. So, surgical approach, if possible, is often considered and usually allows a really diagnosis of solitary plasmacytoma. Furthermore also radiotherapy and chemotherapy are considered. Median survival rate of a solitary plasmacytoma is longer than patients with that with multiple myeloma [52, 53], because of the absence of diffused bone marrow alterations, and of reduced involvements of kidney damages and calcium metabolism. However, full clinical remission is unusual. Prognosis of solitary plasmacytoma could be worse if recurrence is present as in case of its evolution toward systemic disease (multiple myeloma) [9]. Also pharmacological toxicity should be considered in patients treated with Melphalan and Prednisone protocol (those with acute leukemia, other oncological disorders seen as well as toxicity). A recent case report underlined a possible therapeutic support of chemotherapy induced amyloidosis in multiple myeloma [54, 55].

REFERENCES


СОЛИТАРНАЯ ПЛАЗМОЦИТОМА И ЕЕ ОТЛИЧИЯ ОТ МНОЖЕСТВЕННОЙ МИЕЛОМЫ

Солитарная плазмоцитома — опухоль, состоящая из плазматических клеток, — является локальным заболеванием костной ткани и этим отличается от множественной миеломы (системного неопластического процесса на плазматических клетках). Несмотря на солитарную плазмоцитому предшествует развитию множественной миеломы. Клинические проявления солитарной плазмоцитомы относятся к одиночной локализации на поврежденной кости, в то время как лабораторные показатели могут быть сходными с таковыми при множественной миеломе (наличие М-градиента, дисфункция почек, изменений содержания кальция в крови, повышенный уровень β-2-микроглобулина). Однако развитие солитарной плазмоцитомы может не сопровождаться изменениями лабораторных показателей и одновременным возникновением таких клинических осложнений, как почечная недостаточность, иммунологические нарушения с тенденцией к развитию инфекционных заболеваний и/или аутоиммунных заболеваний, нервологические и гематологические расстройства, амилоидоз, POEMS). Этим объясняется тот факт, что прогноз при солитарной плазмоцитоме благоприятней, чем таковой при множественной миеломе. Ключевые слова: солитарная плазмоцитома, множественная миелома.