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ORIGINAL ARTICLE

Peroxiredoxin I is differentially expressed in multiple myelomas and in plasmablastic lymphomas

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BACKGROUND: Plasmablastic lymphoma (PBL) and multiple myeloma (MM) are B cell-derived malignancies that share many morphologic and immunophenotypic traits, making the differential diagnosis particularly complicated. We have recently demonstrated that peroxiredoxin I (PrdxI) is expressed in plasma cells but not in B lymphocytes, suggesting that its expression is development-associated.

AIM: To analyze PrdxI expression in PBL and in MM in order to study its utilization as an additional diagnostic molecular tool.

METHODS AND RESULTS: Eight cases of PBL and nine of MM were studied by immunohistochemistry. We have demonstrated that PrdxI expression is closely connected with the immunoglobulin production capacity of the cells, which means high in MM, but absent in PBL cases, except one, wherein few cells were stained.

CONCLUSIONS: We hypothesize PrdxI as a component of the unfolded protein response (UPR), an adaptive pathway essential for plasma cell differentiation. As we have not detected immunoglobulin in our PBL cases, we suggest that UPR was not activated in the cells, accounting for the impediment of the developmental process, and for the inhibition of PrdxI expression observed. PrdxI could be considered an additional plasma cell functional marker and could also be speculated as a therapeutic target in the treatment of MM.

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Keywords: peroxiredoxins; multiple myeloma; plasmablastic lymphoma; plasma cell tumor; unfolded protein response

Introduction

Among the B-cell lineage malignancies resulting from the proliferation of final differentiation-related cells, multiple myeloma (MM) and plasmablastic lymphoma (PBL) share several morphologic and immunophenotypic features, which makes the differential diagnosis particularly problematic (Vega *et al*, 2005).

Multiple myeloma is the second most prevalent hematological cancer. It is a multi-focal monoclonal plasma-cell proliferation in bone marrow, manifested by: (i) anemia and immunosuppresion, caused by loss of normal hematopoietic stem cell function, (ii) organ damage, because of excess monoclonal immunoglobulin secretion, and (iii) osteolytic lesions besides hypercalcemia, because of detached bone metabolism (Ludwig, 2005; Hideshima *et al*, 2007). Clinically, this tumor presents usually a highly malignant behavior. Bone marrow biopsy shows an overload of plasma cells occurring in a variable maturity range, from immature or plasmablasts, to mature forms, indistinguishable from normal plasma cells (Goasguen *et al*, 1999). These cells frequently exhibit immunophenotypic profile of differentiated plasma cells, including absent expression of the B-cell marker CD20 and strong reactivity with plasma-cell-associated antigens such as CD38, CD138, and VS38c (Bataille *et al*, 2006). The most common immunoglobulin produced is IgG, followed by IgA, while IgD, IgE, and IgM are rare. When the plasma cell tumor occurs as a solitary lesion, it is called plasmacytoma and may arise in bone or soft tissues, most commonly of the head and neck or lungs.

Plasmablastic lymphoma was initially described as a distinct subtype of diffuse large B-cell lymphoma, mainly diagnosed in patients infected with the human immunodeficiency virus (HIV), typically involving the mucosa of the oral cavity, with highly aggressive clinical behavior (Delecluse *et al*, 1997; Colomo *et al*, 2004; Teruya-Feldstein, 2005). These tumors are characterized by a predominant proliferation of immunoblasts and plasmablasts unexpectedly exhibiting plasma cell immunophenotype (Delecluse *et al*, 1997; Colomo *et al*, 2004), which complicates the differential diagnosis when

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they are compared with plasmacytomas and MMs (Vega *et al*, 2005). Cellular morphology cannot define the diagnosis as well, as the malignant cells of these tumors present in a variable and somewhat overlapping maturity range (Vega *et al*, 2005).

At last, the distinction between PBL and plasma cell malignancies is prominently based on clinical correlation. The detection of excess-single immunoglobulin (M protein) in blood or excess light chains (Bence–Jones proteins) in urine, and the description of bone lytic lesions, hypercalcemia or anemia, favors diagnosis of plasma cell neoplasm, while immunosuppression, especially AIDS-related, is much more frequently associated with PBL (Colomo *et al*, 2004), as well as the presence of Epstein–Barr virus (EBV) (Vega *et al*, 2005).

Peroxiredoxin I (PrdxI) is one of the six isoforms of the mammalian peroxiredoxin family, a set of proteins involved in the detoxification of peroxides and peroxynitrite with reducing equivalents provided through the thioredoxin system (Rhee *et al*, 1999; Hofmann *et al*, 2002; Wood *et al*, 2003). All Prdx proteins are characterized by the presence of a conserved cysteine residue in the *N*-terminal region, which is responsible for catalysis. PrdxI may also function as a molecular chaperone, preventing protein aggregation, a function achieved by its structural switch from the dimer to a high-molecular-weight multimer (Wood *et al*, 2003; Jang *et al*, 2004; Moon *et al*, 2005; Lee *et al*, 2007). Prdxs have been implicated in a range of cellular processes such as proliferation, differentiation, and cellular signaling (Kang *et al*, 2005). We have recently demonstrated that PrdxI is expressed in the terminally differentiated plasma cells, but not in B lymphocytes (Demasi *et al*, 2007), suggesting that its expression is development-associated. In this manner, we have analyzed PrdxI expression in neoplastic cells from PBL and MM cases. Our results support the inclusion of PrdxI in the antigenic profile to assist the diagnostic differentiation between PBL and plasma cell tumors.

Materials and methods

Tissue samples

Eight cases of PBL and nine of MM were identified from the files of the pathology departments at the São Leopoldo Mandic Dental Research Center and at the University of São Paulo, Brazil. This work has been approved by the ethical committees of the mentioned Research Centers and it was developed with the consent of the donating subjects. Tissue samples were available as formalin-fixed and paraffin-embedded material. Hematoxylin and eosin-(H&E) stained sections were examined and tumors were classified on the basis of their morphologic features and clinical information, obtained to the extent possible. We only included in this study the cases of MM which were confirmed with subsequent clinical data.

Immunohistochemistry

Sections (4 μm) from the paraffin blocks were deparaffinized in xylene, rehydrated through descending ethanol series and were submitted to heat-induced antigen retrieval. After that, sections were immersed in 0.3% hydrogen peroxide in methanol and incubated with primary antibody. The antibodies used were specific for: PrdxI (1:500) (Alexis Corp., Lausen, Switzerland), CD20 (1:500), LCA (1:600), VS38c (1:100), IgG (1:100), IgA (1:10), κ (1:100) and λ (1:80) (Dako Corp., Glostrup, Denmark). Peroxidase-linked secondary antibody and diaminobenzidine tetrahydrochloride (DAB) (Peroxidase Envision Kit, Dako Corp., Carpinteria, USA) were used to detect specific binding. The sections were counterstained with hematoxylin, dehydrated, and mounted. Digital photomicrography were obtained with a Zeiss Axioskop 2 plus microscope equipped with AxioCam digital camera and Axiovision application software (Carl Zeiss, Gottingen, Germany).

Results

Eight cases of PBL and nine of MM have been studied. Table 1 lists some clinical features of the patients. Six (numbers 1–6) of the eight patients presenting PBL were infected by HIV in association with EBV; in the remaining two these infections were not determined.

All PBL cases showed similar histological features, consisting of predominant proliferation of large lymphoid cells with plasmablastic traits, variable proportion of immunoblasts, and relatively few smaller cells with plasmacytic differentiation. The tumors displayed a diffuse pattern of growth interspersed by macrophages, which often gave rise to a starry sky appearance. The nuclei were large, more or less eccentrically located, usually with single prominent central nucleolus.

Tissue biopsies from MM patients demonstrated neoplastic plasma cells predominantly presented in their mature forms of small oval cells with round eccentric nuclei, coarsely condensed chromatin, abundant basophilic cytoplasm, and a prominent pale perinuclear Golgi zone. Two (patients number 5 and number 8) of the eight cases presented a comparatively higher proportion of large immature cells and were considered as plasmablastic myelomas (Vega *et al*, 2005).

The results of immunophenotypic analyses are summarized in Table 1. All the cases studied, including PBL and MM, displayed homogeneous reactivity to the B cell differentiation classic markers, negative for CD20 and LCA and, positive for VS38c. In contrast, intracytoplasmic IgG expression was detected exclusively in the MM cases. IgA was not detected in any of the cases. Monotypic light chain staining was also demonstrated in all the MM cases, but only in one (patient number 2) of the PBL.

Outstandingly, PrdxI expression was closely associated with immunoglobulin production capacity, even when only light chains were perceived. All MM cases, including those considered as plasmablastic on histological grounds, were positive for PrdxI, with a cell staining proportion higher than 85% (Figure 1, Table 1). In opposition, all the PBL cases were uniformly negative for this protein and the few cells presenting plasmacytic differentiation were still negative for PrdxI (Figure 1). However, in one PBL case

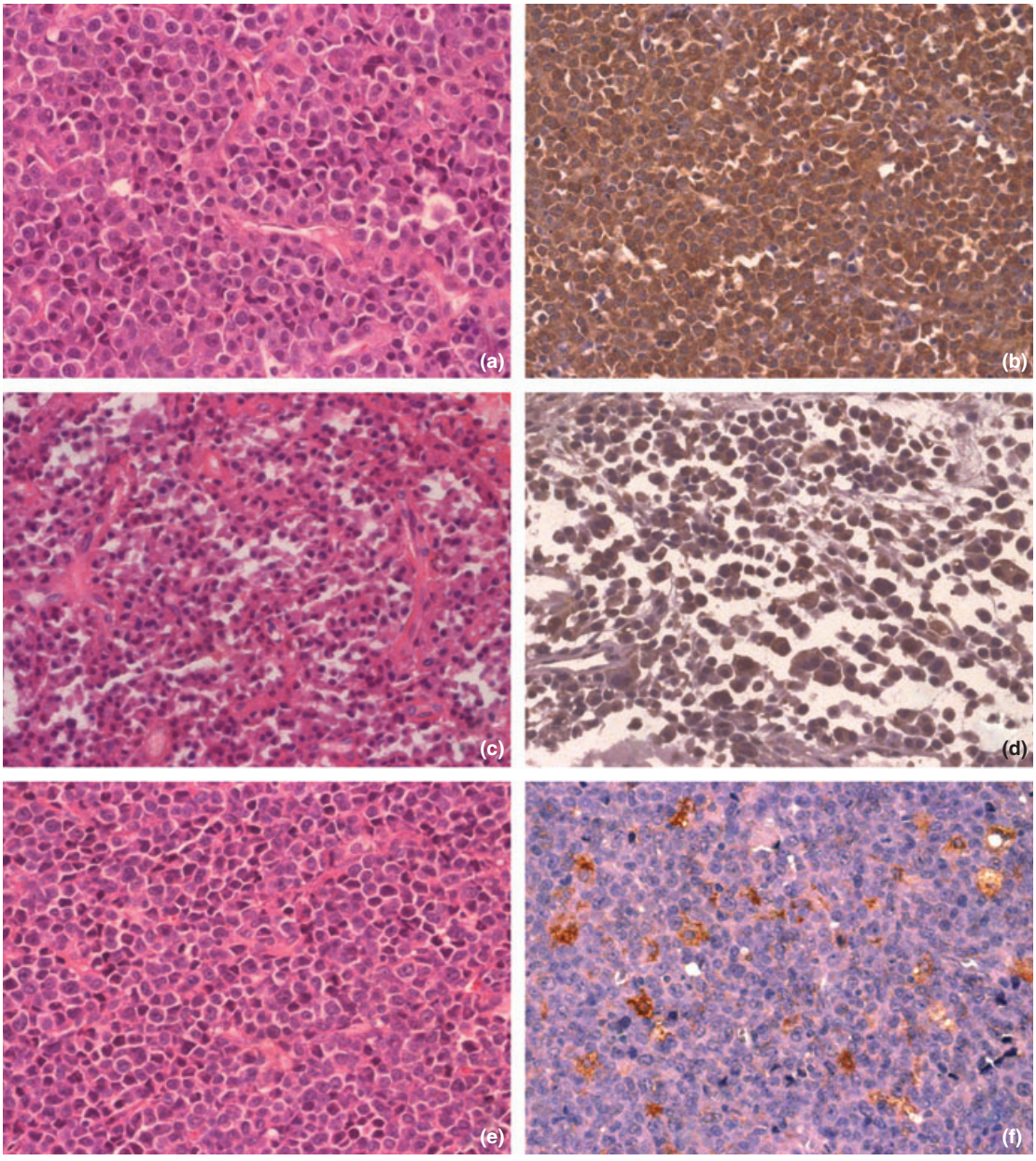

Figure 1 PrdxI expression in multiple myeloma and in plasmablastic lymphoma (PBL) cases and their morphology. (**a, b**) Plasmablastic myeloma. (**a**) Large immature cells with features of plasmablasts are distributed among the predominant plasmacytic cells (H&E). (**b**) Staining with PrdxI-specific antibody, positive for neoplastic cells. (**c, d**) Plasmacytic myeloma. (**c**) The tumor cells have prominent plasmacytic differentiation (H&E). (**d**) Staining with PrdxI-specific antibody, positive for neoplastic cells. (**e, f**) PBL. (**e**) Diffuse infiltrate of large lymphoid cells with plasmablastic traits interspersed by macrophages (H&E). (**f**) Starry sky-like staining with PrdxI-specific antibody, negative for neoplastic cells, positive for macrophages. Original magnifications for all sections: ×400

(patient number 2) a reduced number of cells were stained with anti-PrdxI, which is $<30\%$ against $>85\%$ in MM. Intriguingly, light chains were also detected in this same case, still presenting prominent plasmablastic cellular morphology. Expression of PrdxI was, in addition, observed in the macrophages interspersed among the tumor cells in the majority of the PBL cases (Figure 1). This observation was in agreement with previous demonstrations (Ishii *et al*, 1993) and also provided a positive control of the antibody reactivity.

Discussion

In this study, we have demonstrated that PrdxI is expressed in neoplastic cells from MM, but not in those from PBL. Our PBL cases were all positive for VS38c and negative for CD20 and LCA. These results are in accordance with Vega *et al* (2005) and also with Delecluse *et al* (1997). Even in the cases where cellular morphology could raise the most doubtful diagnosis, such as in the plasmablastic myeloma cases, PrdxI expression revealed the actual differentiation stage of the

Table 1 Clinical and immunophenotypic features of multiple myeloma cases (patients 1–9) and of PBL cases (patients 10–17)

Patient no	*Localization*	*Age (years)*	*Sex*	*CD20*	*LCA*	*VS38c*	*κ*	*λ*	*IgG*	*IgA*	*PrdxI*
Multiple myeloma											
1	Mandible	65	F	−	−	+	+	−	+	−	+
2	Mandible	60	F	−	−	+	+	−	+	−	+
3	Hard palate	26	F	−	−	+	−	+	+	−	+
4	Mandible	56	F	−	−	+	+	−	+	−	+
5	Mandible	56	F	−	−	+	−	+	+	−	+
6	Skull	68	F	−	−	+	−	+	+	−	+
7	Mandible	58	F	−	−	+	−	+	+	−	+
8	Pterygomandibular region	73	M	−	−	+	−	+	+	−	+
9	Mandible	66	M	−	−	+	−	+	+	−	+
PBL											
10	Mandibular gingiva	41	M	−	−	+	−	−	−	−	−
11	Gingiva	49	M	−	−	+	−	+[a]	−	−	+[a]
12	Nasal mucosa	09	M	−	−	+	−	−	−	−	−
13	Mandibular gingiva	40	M	−	−	+	−	−	−	−	−
14	Mandibular gingiva	40	M	−	−	+	−	−	−	−	−
15	Mandibular gingiva	49	F	−	−	+	−	−	−	−	−
16	Maxillary gingiva	40	M	−	−	+	−	−	−	−	−
17	Mandibular gingiva	54	M	−	−	+	−	−	−	−	−

+, expression of the antigen (more than 85% of the cells); −, absence of expression of the antigen; PBL, plasmablastic lymphoma.
[a]Expression of the antigen in less than 30% of the cells.

proliferating cells. Remarkably, the detectability of cytoplasmic immunoglobulin resembled that of PrdxI, strengthening the relationship between PrdxI and immunoglobulin production previously suggested by us (Demasi *et al*, 2007).

Because MM cells produce large amounts of monoclonal immunoglobulin that must be processed within the endoplasmic reticulum (ER), it has been recognized that these cells are under chronic ER stress (Shapiro-Shelef and Calame, 2004; Nakamura *et al*, 2006). The ER is responsible for glycosylation, disulfide bond formation, folding, and assembly of newly-synthesized secretory proteins. Overload of these functions results in accumulation of unfolded proteins, a condition referred to as ER stress, which can lead to cell death (Cenci and Sitia, 2007). Cells respond to such stress by activating adaptive pathways collectively termed the unfolded protein response (UPR), which promotes protein translation attenuation, induction of chaperones to increase the folding capacity, and induction of ER-associated degradation components to prevent the aggregation of accumulating misfolded proteins (Szegezdi *et al*, 2006).

Recent genome-wide studies demonstrated that the UPR also comprises antioxidant and DNA repair enzymes (Shaffer *et al*, 2004; Acosta-Alvear *et al*, 2007), probably to neutralize the reactive oxygen species (ROS) generated as byproducts of the oxidative protein folding (Tu and Weissman, 2004; Benham, 2005; Gross *et al*, 2006). Sustained ER stress was reported to cause prolonged UPR activation and subsequent accumulation of ROS both in yeast and in mammalian cells (Harding *et al*, 2003; Haynes *et al*, 2004). In addition, it was proposed an ER consumption of glutathione to the direct reduction of unstable and improper disulfide bonds (Cuozzo and Kaiser, 1999). The combination of ROS generation and glutathione depletion synergistically increases the potential of oxidative cellular damage.

It was shown that activation of UPR promotes survival of myeloma cells (Nakamura *et al*, 2006). These cells constitutively express high levels of UPR survival components, including the ER resident chaperones GRP78 and GRP94 (Obeng *et al*, 2006). The expression of PrdxI in MM cells could be explained in view of PrdxI as an UPR component, functioning in the elimination of the potentially damaging by-products of disulfide bond formation, or as a chaperone preventing protein aggregation. PrdxI could be even more significant taking into account that its redox cycling does not depend on glutathione but on the thioredoxin system as source of reducing equivalents. Indeed, it was demonstrated that *TSA1*, which encodes the yeast homolog of PrdxI is up-regulated by the yeast UPR in a pathway that has been evolutionarily conserved in higher eukaryotes with few modifications (Kimata *et al*, 2006). The existence of ER stress and UPR in PBL cells is largely unknown, but lack of immunoglobulin production capacity may imply their absence.

The transcription factor X-box binding protein 1 (XBP-1) is a major UPR regulator and it is also in charge of the overall B-cell transformation that accompanies plasmacytic differentiation (Reimold *et al*, 2001; Iwakoshi *et al*, 2003; Shaffer *et al*, 2004). XBP-1 activation is subject to alternative RNA processing by IRE1, an ER-resident kinase and endoribonuclease, resulting in a spliced transcript designated XBP-1s, which is more stable and possesses enhanced transactivation potential (Reimold *et al*, 2001; Iwakoshi *et al*, 2003; Shaffer *et al*, 2004). It has been demonstrated that IRE1 activation in plasma cells and the consequent production of XBP-1s is dependent on biosynthesis and accumulation of unfolded immunoglobulin, imposing that the UPR is an essential component of plasma cell differentiation to support huge level of antibody production (Iwakoshi *et al*, 2003). XBP-1 deficient B cells

from chimeric mice are less differentiated, displaying a severe defect in the generation of plasma cells and impairment in the production of immunoglobulin of all isotypes (Reimold *et al*, 2001).

Abundant XBP-1 expression has been detected in human MM cells (Munshi *et al*, 2004; Carrasco *et al*, 2007). Utilizing a transgenic mouse model, Carrasco *et al* demonstrated that enforced XBP-1s expression in the B cell compartment enhanced B cell proliferative potential and led to the development of MM disease possessing many molecular, cellular, and clinical features similar to those in humans. Thus, chronically increased levels of XBP-1 could undesirably be involved in MM pathogenesis (Carrasco *et al*, 2007). On the other hand, inhibiting XBP-1 genetically in myeloma cells could sensitize them to ER stress-induced apoptosis (Lee *et al*, 2003). So far, no study has investigated XBP-1 expression in PBL cells.

Shaffer *et al* (2004), using human Lymphochip cDNA microarrays, identified a peroxiredoxin family member gene, *PRDX4*, as a gene up-regulated by ectopic expression of XBP-1s in human mature B cell line Raji. The corresponding *PRDX1* cDNA sequence was not present in the Lymphochip used. Anyway, *PRDX1* do possesses the XBP-1 binding sequence ACGT (Kanemoto *et al*, 2005) in its promoter, which is an indicator of its regulation by this transcription factor.

Considering the phenotypic similarities between XBP-1 deficient and PBL cells and the lack of immunoglobulin observed in our PBL cases, we could speculate that absence of UPR and defective XBP-1 activation could account for the impediment of the developmental process, as well as for the inhibition of PrdxI expression observed in the PBL cells. Moreover, expression of *SDC1*, encoding syndecan-1 (CD 138), does not require XBP-1 (Shaffer *et al*, 2004), consistent with the detection of this antigen in PBL cells. Although some studies have demonstrated occasional immunoglobulin detection in PBL cases (Delecluse *et al*, 1997; Colomo *et al*, 2004), we suggest that these outlier cases could have intermediate characteristics and could represent distinct clinical entities. In fact, excess M protein in blood, or excess Bence–Jones proteins in urine are clinical features much more related to MM, than to PBL. Further studies are necessary to confirm all these speculations.

Our results propose PrdxI as an additional plasma cell functional marker which frequently indicates not only the synthesis of immunoglobulin but also the stress caused by this acquired specialized function at the very final stage of this process. It was suggested that myeloma cells are inherently sensitive to proteasome inhibitors, shown to block the IRE1-XBP-1 pathway and induce apoptosis (Obeng *et al*, 2006, Lee *et al*, 2003, Koong *et al*, 2006). Likewise, it has been demonstrated that myeloma cells are also more susceptible to chemotherapeutic agents known to induce oxidative stress, including imexon (Dvorakova *et al*, 2000), motexafin gadolinium (Evens *et al*, 2005), arsenic trioxide (Miller *et al*, 2002), and chaetocin (Isham *et al*, 2007). Thus, the inhibition of either the expression or the activity of PrdxI combined with existing cytotoxic agents known to induce ER and/or oxidative stress, might be considered as a new therapeutic strategy to treat MM. In fact, targeting Prdxs has been suggested as a promising approach to treat different kinds of malignancies (Chen *et al*, 2002, Wang *et al*, 2005, Zhang *et al*, 2005, Kang *et al*, 2005, Chen *et al*, 2006, Neumann and Fang, 2007). In conclusion, our observations suggest that PrdxI, besides as an additional plasma cell marker, could also be considered as a therapeutic target.

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Competing interests

None.

Author Contributions

Ana Demasi and Vera Araujo contributed to the research design. Ana Demasi, Cristiane Furuse contributed to the acquisition and analysis of data. Ana Demasi, Vera Araujo, Marina Magalhaes and Ney Araujo contributed to the interpretation of the data. Ana Demasi contributed in drafting the paper. Vera Araujo, Jose Junqueira and Ney Araujo worked on the critical revision of the paper.

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