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INVITED REVIEW
HOT TOPIC

Plasmablastic lymphoma: a review

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Plasmablastic lymphoma (PBL) has been recently characterised as an aggressive subtype of non-Hodgkin's lymphoma, most frequently arising in the oral cavity of HIV-infected patients. To date, approximately 60 cases fulfilling the clinico-pathological characteristics of PBL have been reported. PBLs are composed of large cells with eccentrically located nuclei and deeply basophilic cytoplasm with a paranuclear hof. The tumour cells are invariably immunoreactive for the plasma cell marker CD138, and show monoclonal rearrangement of the immunoglobulin heavy chain gene (IgH) and/or clonal restriction of the Ig light chain (IgL) gene expression in most of the cases. Similar to other types of AIDS-related lymphomas, there is evidence that Epstein–Barr virus and Kaposi-sarcoma associated Human Herpes Virus 8 may play a relevant role in the pathogenesis of PBL. PBL patients have been treated heterogeneously, with a combination of chemotherapy, radiotherapy and/or surgery, and their prognosis is usually poor, with a death rate of approximately 60% at 1 year.

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Background

In 1997, Stein and coworkers (Delecluse *et al*, 1997) reported a series of aggressive non-Hodgkin's lymphomas (NHLs) arising in the oral cavity of human immunodeficiency virus (HIV)-positive patients. These tumours were composed of large cells with plasma cell differentiation, and were called plasmablastic lymphoma (PBL) (Figure 1). For its peculiarities PBL was acknowledged as a specific subtype of immunodeficiency-associated lymphoproliferative disorder by the World Health Organization (Gatter *et al*, 2001; Raphael *et al*, 2001). Following the original description, approximately 60 further cases fulfilling the clinico-pathological characteristics of PBL have been reported (Table 1) (Delecluse *et al*, 1997; Brown *et al*, 1998; Pruneri *et al*, 1998; Porter *et al*, 1999; Carbone *et al*, 2001; Lin *et al*, 2001, 2004; Robak *et al*, 2001; Borrero *et al*, 2002; Flaitz *et al*, 2002; Gaidano *et al*, 2002; Nasta *et al*, 2002; Chetty *et al*, 2003; Nguyen *et al*, 2003; Nicol *et al*, 2003; Ojanguren *et al*, 2003; Cioc *et al*, 2004; Colomo *et al*, 2004; Hausermann *et al*, 2004; Lester *et al*, 2004; Schichman *et al*, 2004; Teruya-Feldstein *et al*, 2004; Cattaneo *et al*, 2005; Deloose *et al*, 2005; Dong *et al*, 2005; Jordan *et al*, 2005; Radhakrishnan *et al*, 2005; Scheper *et al*, 2005; Tzankov *et al*, 2005; Vega *et al*, 2005; Verma *et al*, 2005; Arbiser *et al*, 2006; Folk *et al*, 2006; Garcia *et al*, 2006; Lee *et al*, 2006; Liu *et al*, 2006; Tavora *et al*, 2006; Armstrong *et al*, 2007; Dawson *et al*, 2007; Desai *et al*, 2007; Masgala *et al*, 2007; Miller *et al*, 2007; Redmond *et al*, 2007).

It has been proposed that Epstein–Barr virus (EBV) and Kaposi-sarcoma associated Human Herpes Virus 8 (HHV8) may play a relevant role in the pathogenesis of PBL (Carbone and Gloghini, 2008), similar to primary effusion lymphoma (PEL), another type of HIV-related NHL with plasmablastic features. PBL shows morphological, phenotypical and molecular features of terminally differentiated B-cells: the neoplastic cells have eccentrically located nuclei and deeply basophilic cytoplasm with a paranuclear hof, and typically express low or absent levels of leucocyte common and B-cell associated antigens. By contrast, they are invariably immunoreactive for CD138, a marker of the terminally differentiated B-cells. As expected, monoclonal rearrangement of the immunoglobulin heavy chain gene (IgH) and/or clonal restriction of the Ig light chain (IgL) gene expression is detectable in most of the cases (Delecluse *et al*, 1997; Pruneri *et al*, 1998; Lin *et al*, 2001, 2004; Robak *et al*, 2001; Gaidano *et al*, 2002; Nasta *et al*, 2002; Nicol *et al*, 2003; Ojanguren *et al*,

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Table 1 Clinico-pathological features of the reported cases of plasmablastic lymphoma

Study	n	*Sex*	*Age*	*Location*	*HIV*	*Treatments*	*Follow up (months)*
Delecluse *et al* (1997)	16	14 M, 2 F	27–75	Oral cavity (16)	15/16	6 chemotherapy/ 4 radiotherapy/4 chemotherapy and radiotherapy/1 refused/1 NA	2 alive (8, 18)/9 dead (1–16)/4 lost to follow-up/1 NA
Brown *et al* (1998)	1	M	35	Oral cavity	1/1	Chemotherapy	Alive (48)
Pruneri *et al* (1998)	1	F	53	Stomach	0/1	Chemotherapy	Alive (19)
Porter *et al* (1999)	1	M	36	Oral cavity	1/1	Chemotherapy	Alive (24)
Carbone *et al* (2001)	7	NA	NA	NA	7/7	NA	NA
Lin *et al* (2001)	1	M	47	Lung	1/1	Chemotherapy	Alive (9)
Robak *et al* (2001)	1	F	57	Mandible	1/1	Chemotherapy	Dead (6)
Borrero *et al* (2002)	1	M	36	Oral cavity	1/1	NA	NA
Flaitz *et al* (2002)	1	M	50	Oral cavity	1/1	Chemotherapy and radiotherapy	Dead (9,5)
Gaidano *et al* (2002)	12	10 M, 2 F	25–68	Oral cavity (12)	12/12	4 chemotherapy and HAART/6 chemotherapy/2 NA	3 alive (26–54)/7 dead (1–28)/2 NA
Nasta *et al* (2002)	1	M	44	Mediastinum		Chemotherapy and HAART	Dead (6)
Chetty *et al* (2003)	4	1 M, 3 F	23–56	1 anorectal/1 perianal/1 anal/1 nasal cavity	4/4	1 chemotherapy/2 NA/1 not done	1 alive (7)/2 lost to follow up/1 dead(< 1)
Nguyen *et al* (2003)	1	M	42	Nasal cavity	0/1	Chemotherapy and radiotherapy	Alive (6)
Nicol *et al* (2003)	1	F	68	Skin	0/1	Chemotherapy and radiotherapy	Alive (9)
Ojanguren *et al* (2003)	2	2 M	30–57	Sacrococcigeal cyst, perianal	1/2	2 chemotherapy	1 alive (40)/1 dead (6)
Cioc *et al* (2004)	4	4 M	31–51	Oral cavity (4)	4/4	1 chemotherapy, radiotherapy and HAART/3 NA	1 alive (6)/3 NA
Colomo *et al* (2004)	39	28 M, 11 F	11–86	7 oral cavity/1 oral cavity and CNS/1 oral cavity, orbit, eyelid, skin and maxilla/2 oral cavity, maxillary sinus and bone marrow/1 oral cavity and lymph node/1 maxillary sinus and bone marrow/1 maxillary sinus, bone marrow and lymph node/1 maxillary sinus, orbit and nasal cavity/1 maxillary sinus and large bowel/2 skin/1 lymph node, pleural effusion and mediastinal mass/1 bone marrow/2 soft tissue sacrum and lymph node/9 lymph node/1 anal mass/1 gastrointestinal tract, liver, ascites/1 rectum/1 testis/1 nasal cavity/1 small and large bowel	21/37	NA	7 alive (4–40)/13 dead (1–28)/21 NA
Hausermann *et al* (2004)	1	M	44	Skin	1/1	Chemotherapy and antiretroviral treatment	Alive (20)
Lester *et al* (2004)	2	2 M	33–50	Oral cavity (2)	2/2	2 chemotherapy and HAART	2 alive (10,25)
Lin *et al* (2004)	1	M	82	Lymph node	0/1	Chemotherapy	Alive (6)
Schichman *et al* (2004)	1	M	41	Nasal sinus, testicles, bones	1/1	Chemotherapy and radiotherapy	Alive (24)

Table 1 Continued

Study	n	*Sex*	*Age*	*Location*	*HIV*	*Treatments*	*Follow up (months)*
Teruya-Feldstein *et al* (2004)	12	12 M	23–73	1 anal canal/1 scrotum/2 rectum and bone/1 stomach/2 colon/1 mandible/1 skin/1 multiple bone/1 neck mass/1 lung and liver	6/11	5 chemotherapy and HAART/1 chemotherapy, radiotherapy and HAART/5 chemotherapy/1 surgical resection and chemotherapy	7 alive (7–27)/5 dead (1–12)
Cattaneo *et al* (2005)	3	3 M	35–37	3 Hard palate	3/3	1 chemotherapy, 2 chemotherapy and radiotherapy	1 alive (26)/2 dead (18–27)
Deloose *et al* (2005)	26	24 M, 2 F	23–57	4 stomach/3 colon/9 lymph node/1 mediastinum/1 CNS/1 pharynx/1 small bowel/1 skin/1 tonsil/2 oral cavity/1 anus/1 testis	26/26	NA	NA
Dong *et al* (2005)	14	12 M, 2 F	28–44	4 oral cavity/1 pharynx/2 skull and sculp/1 soft tissue/1 anal mucosa/1 small bowel, lymph node mesenteric and perigastric/1 spermatic cord/2 lymph node/1 lymph node inguinal, pelvic and spleen	14/14	1 radiotherapy/6 chemotherapy/3 chemotherapy and radiotherapy/1 steroid/1 none/2 NA	1 alive (72)/11 dead (<1–24)/2 NA
Jordan *et al* (2005)	1	M	63	Skin	1/1	NA	NA
Radhakrishnan *et al* (2005)	1	M	7	Oral cavity	1/1	NA	NA
Scheper *et al* (2005)	1	M	49	Oral cavity	0/1	NA	Lost to follow-up
Tzankov *et al* (2005)	1	M	63	Oral cavity	0/1	NA	NA
Vega *et al* (2005)	9	8 M, 1 F	23–58	5 oral/2 pharynx/1 anus/1 lymph node	9/9	NA	NA
Verma *et al* (2005)	1	F	38	Skin	0/1	Surgical resection and radiotherapy	Alive (32)
Arbiser *et al* (2006)	1	F	39	Skin	NA	Chemotherapy	Dead (NA)
Garcia *et al* (2006)	15	NA	NA	Oral cavity (15)	15/15	NA	NA
Folk *et al* (2006)	5	4 M, 1 F	35–55	Oral cavity (5)	3/3	1 chemotherapy and HAART/4 NA	1 alive (NA)/3 dead (NA)/1 lost to follow-up
Lee *et al* (2006)	1	M	66	Oral cavity	0/1	Chemotherapy and radiotherapy	Dead (8)
Liu *et al*, 2006	1	M	56	Subcutis	1/1	Chemotherapy and HAART	Alive (5)
Tavora *et al* (2006)	1	M	33	Anus	1/1	NA	NA
Armstrong *et al* (2007)	1	M	35	Oral cavity	1/1	Chemotherapy and HAART	Alive (1)
Dawson *et al* (2007)	1	M	36	Oral cavity	1/1	Chemotherapy and HAART	Dead (14)
Desai *et al* (2007)	1	M	30	Oral cavity	1/1	NA	NA
Masgala *et al* (2007)	1	F	67	Visceral cranium, cervix and thorax	0/1	Chemotherapy	Dead (23)
Miller *et al* (2007)	1	M	65	Heart	0/1	Not done (diagnosis at dead)	Dead
Panos *et al* (2007)	1	F	20	Oral cavity	1/1	Chemotherapy and HAART	Alive (61)
Redmond *et al* (2007)	1	M	32	Paravertebral, skin	0/1	Chemotherapy and radiotherapy	NA

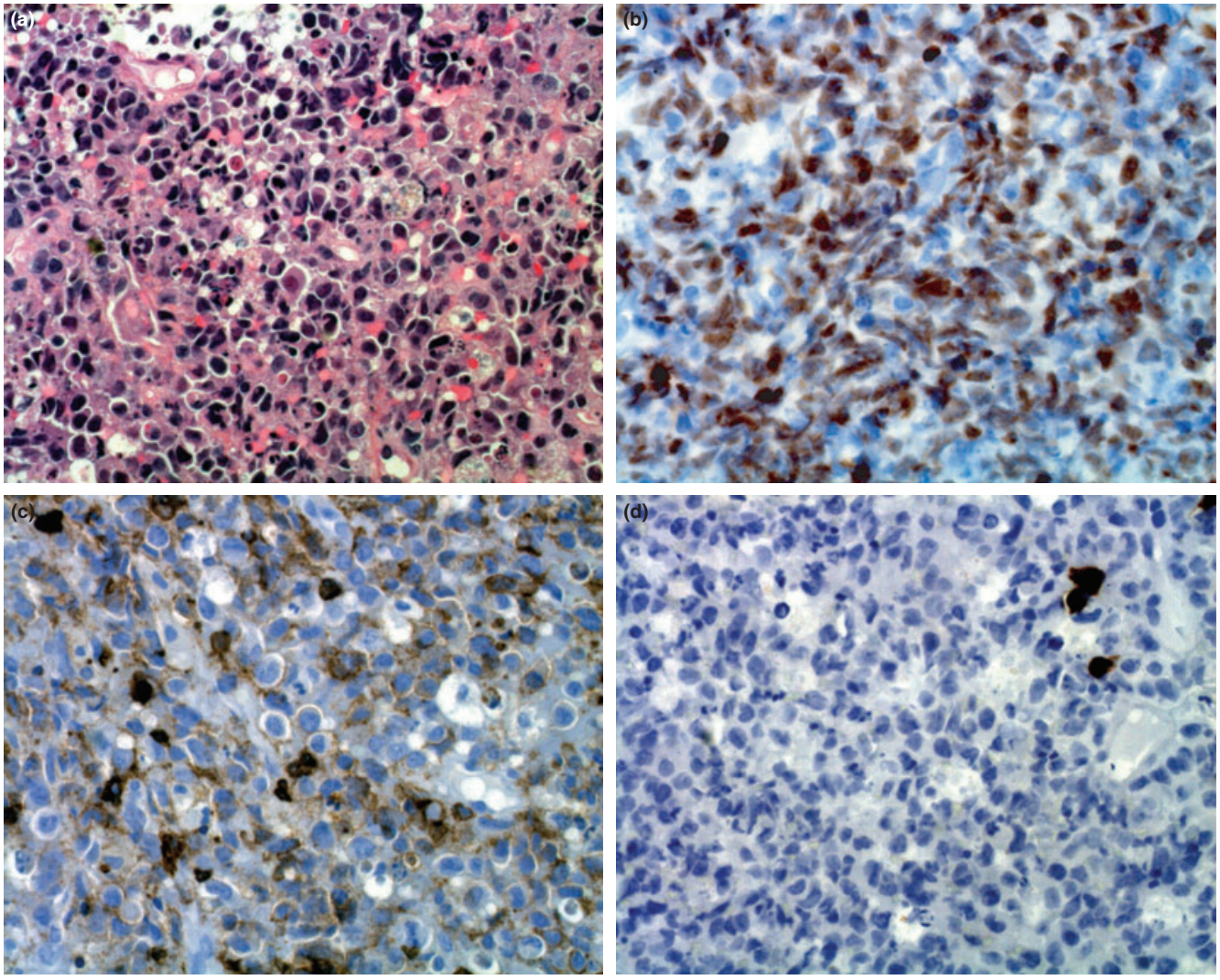

Figure 1 Typical morphological and immunophenotypic features of plasmablastic lymphoma. The tumour is composed of large and scarcely cohesive cells with abundant cytoplasm and eccentrically placed nuclei, resembling immature plasma cells (**a**: haematoxylin–eosin, ×40), which demonstrate consistent nuclear immunoreactivity for MUM-1 (**b**: anti-MUM-1 immunostain, ×40), occasional and focal CD45-positivity (**c**: anti-CD45RB immunostain, ×40) despite the lack of immunoreactivity for CD79a (**d**: anti-CD79a immunostain, ×40). Mature non-neoplastic plasma cells demonstrate CD79a immunoreactivity, providing adequate internal positive control

2003; Hausermann *et al*, 2004; Tzankov *et al*, 2005; Masgala *et al*, 2007). PBL patients have been treated heterogeneously with a combination of chemotherapy with alkylants, and/or radiotherapy, and their prognosis is usually poor, regardless of the primarily involved site (oral and extra-oral) and the clinical setting (HIV-infection or immunocompetence).

Epidemiology

The association between PBL and immunosuppression has been clearly ascertained. Indeed, the overwhelming majority (81%) of the cases arise in the setting of HIV infection, so that PBL accounts for 2.6% of all HIV-associated NHLs (Carbone, 2002). Furthermore, approximately one-third (33%) of HIV-negative cases arise in immunodeficient patients following solid organ transplantation or steroid therapy. The association between HIV infection and lymphomagenesis has been extensively analysed (Carbone, 2003). It has been proposed that AIDS-related lymphomas may develop along four pathogenetic pathways involving EBV and HHV8 infection, as well as c-myc, p53 and bcl-6 gene aberrations. Accordingly, EBV infection has been detected in 76% of the 180 PBL cases analysed by PCR and/or immunohistochemistry for the EBV-encoded protein LMP-1. By contrast, the actual prevalence of HHV8 infection in PBL is more controversial, possibly depending on the sensitivity of the techniques used. In particular, HHV8 DNA was found in 37% of the cases (21/57) analysed by DNA-PCR, while immunoreactivity for HHV8-encoded proteins was detected in a smaller subset of patients (16/96 = 17%) (Delecluse *et al*, 1997; Carbone *et al*, 2001; Dong *et al*, 2005). HHV8 plays a major role in the pathogenesis of a number of HIV-related tumours, namely Kaposi

sarcoma (KS), Burkitt's lymphoma, nasopharyngeal carcinoma, PEL and multicentric Castleman's disease (MCD)/MCD-associated PBL. HHV-8 infected cells express latent gene products, including LNA1, cyclins and FLICE inhibitory proteins, which may promote cell growth and impair apoptosis, eventually leading to neoplastic transformation. The viral gene interleukin 6, BCL2 homologues and a viral G-protein-coupled-receptor (v-GPCR), homologous to the human interleukin 8 receptor, have also been proposed to play an oncogenic role (Carbone and Gloghini, 2008).

Clinical features

Plasmablastic lymphoma was originally described as a disease specifically involving the oral cavity of immunodeficient patients. Following the first report, a number of cases have been reported in extra-oral sites, including the maxillary sinus, nasopharynx, stomach, small bowel, anus, lung, skin, soft tissues, heart and the spermatic cord (Dong *et al*, 2005), as well as in immunocompetent patients. Furthermore, several cases of primarily nodal PBL have also been described. Overall, the oral cavity represents the primary site of origin in 51% of the cases, while 20% of extra-oral PBL involve the lymph nodes.

No significant differences in age and gender have been reported between oral and extra-oral PBL. The peak of incidence for the oral and extra-oral types occurs at 41 years (range 7–86 years) and 46 years (range 11–86 years), respectively, and both are more common in males (the M/F ratio is 5.7:1 for the oral type and 4:1 for the extra-oral type).

Oral type PBL arises in HIV-positive patients in the overwhelming majority (90%) of the cases, and usually presents with a localised (62% of the cases are at stage I at diagnosis), painful and rapidly growing neoplastic mass, which may infiltrate the adjacent bone, a clinical picture that may be misinterpreted as KS.

Extra-oral PBL occurs less frequently in the immunodeficiency setting (70% of cases) and is more commonly disseminated (57% of the patients are at stage IV) at diagnosis. PBL patients have been treated heterogeneously, and well-defined treatment guidelines are still lacking. Chemotherapy, radiotherapy with or without surgical excision or a combination of both chemotherapy and radiotherapy have been used depending on the stage of the disease, the presence of systemic symptoms or the association with HIV infection. In particular, of the 68 patients for whom treatment information is available, 75% received only chemotherapy containing alkylating agents, 20.5% a combination of radiotherapy and chemotherapy, and 4.5% radiotherapy only.

The prognosis of PBL patients is usually poor, regardless of the site of origin, although the data from the literature are frequently incomplete and largely based on single case reports. In particular, a meta-analysis of the 98 patients for whom complete follow-up data are available provides evidence that the prevalence of disease-related deaths is 59.6% in a mean period of 10.4 months from diagnosis for the oral type and 58.6% in a mean period of 6.2 months for the extra-oral type.

The death rate for the 68 HIV-infected patients with available follow-up data is 53% in a mean period of 10.4 months from diagnosis. Interestingly, it has been suggested that the addition of a highly active antiretroviral therapy (HAART) to chemotherapy is capable of significantly improving the prognosis: a meta-analysis of 52 HIV-associated PBL patients with complete therapeutic and clinical data showed that the surviving fraction was 85% (17/20) and 28% (9/32) for patients receiving or not HAART in addition to chemotherapy and/or radiotherapy.

Morphological features

Plasmablastic lymphoma typically is characterised by a monomorphic proliferation of large, round or oval cells, with abundant cytoplasm and eccentrically placed nuclei, a single prominent central nucleolus or several peripherally located nucleoli, growing in a diffuse pattern. Apoptotic bodies and mitotic figures are frequent and numerous macrophages with tingible bodies are easily detectable, leading to a 'starry-sky' appearance.

Recently, Colomo *et al* (2004) identified a morphologic variant of classical PBL, in which smaller lymphocytes with plasmacytic differentiation and mature plasma cells are intermingled with plasmablasts, and named it PBL with plasmacytic differentiation.

Immunophenotype

Plasmablastic lymphoma has a terminally differentiated B-cell immunophenotype, characterised by minimal or absent expression of leucocyte common antigen (CD45) and B-cell antigens (CD20 and CD79a). By contrast, the tumour cells in PBL are invariably immunoreactive for CD138, a member of the transmembrane heparan sulphate proteoglycan family, that plays a role in plasma cell adherence to bone marrow stromal matrix (Ridley *et al*, 1993). Strong expression of the post germinal centre-associated markers MUM1 and CD38 is usually present (Nicol *et al*, 2003; Vega *et al*, 2005), and monotypic light chain expression is frequently observed (Colomo *et al*, 2004; Dong *et al*, 2005; Vega *et al*, 2005; Redmond *et al*, 2007), resulting in a phenotypic pattern nearly identical to that of plasma cell myeloma (Vega *et al*, 2005). The absence of PAX-5, a nuclear factor present in all mature B cells from the precursor B-cell stage and lost in terminally differentiated cells, is an additional evidence of plasma cell differentiation (Dong *et al*, 2005; Vega *et al*, 2005). PRMD1/BLIMP1, a fundamental regulator protein of terminal B cell differentiation, is invariably expressed in oral PBL (Garcia *et al*, 2006). Aberrant expression of the T-cell markers CD3 and CD4 has also been reported (Tzankov *et al*, 2005; Vega *et al*, 2005; Redmond *et al*, 2007). The actual prevalence of CD56 expression, a cell surface adhesion glycoprotein belonging to the immunoglobulin family, involved in direct cell–cell adhesion and in organogenesis, still is a matter of debate: Colomo

et al (2004) found CD56 immunoreactivity only in one out of the 18 analysed cases, and suggested to use this marker for distinguishing PBL from extramedullary plasma cell myeloma. Unfortunately, these data were not confirmed by the study of Vega *et al* (2005), who found CD56 expression in a large proportion (5/9 cases = 56%) of the PBL analysed. Likewise, it was proposed that immunoreactivity for cyclin D1 may be an adjunct for differentiating PBL, which usually is non-immunoreactive, from plasma cell myeloma, which expresses cyclin D1 in up to 25% of the cases (Pruneri *et al*, 2000; Colomo *et al*, 2004).

The ALK gene, which encodes for a transmembrane receptor tyrosine kinase, is translocated to different partner genes on chromosomes 1-3 and 17 in 60–80% of anaplastic large cell T-NHL. The most common translocation is the t(2;5)(p23;q35) that juxtaposes ALK to the nucleophosmin (NPM) gene, leading to the expression of the NPM/ALK fusion protein. It has been recently reported that full-length ALK may also be expressed in a rare variant of diffuse large B-cell lymphoma (DLBCL) (Delsol *et al*, 1997), sharing with PBL some morphological (plasmablastic differentiation) and phenotypical (absence of B-cell associated antigens) features (Gatter *et al*, 2001; Raphael *et al*, 2001). Immunoreactivity for the NPM/ALK protein was reported in three cases of extra-oral PBL, also carrying the t(2;5)(p23;q35) (Adam *et al*, 2003; Onciu *et al*, 2003) gene mutation. Although it cannot be ruled out that the ALK protein may be rarely expressed in bona fide PBL, it is conceivable that these cases may rather represent DLBCL with ALK expression (Delsol *et al*, 1997).

Genetics

The overwhelming majority (26/27 analysed cases) of PBL show rearrangement of the immunoglobulin heavy chain gene (Delecluse *et al*,1997; Pruneri *et al*, 1998; Lin *et al*, 2001; Robak *et al*, 2001; Borrero *et al*, 2002; Gaidano *et al*, 2002; Nasta *et al*, 2002; Nicol *et al*, 2003; Ojanguren *et al*, 2003; Hausermann *et al*, 2004; Tzankov *et al*, 2005; Arbiser *et al*, 2006; Liu *et al*, 2006; Masgala *et al*, 2007). The single case lacking IgH rearrangement, bore rearrangement of the Ig light chain gene (Lin *et al*, 2004). Gaidano *et al* (2002) also carried out a sequencing analysis of the IgVH genes in 10 cases of HIV-associated PBL, and found a somatic hypermutation in four of them, suggesting that PBL may be a molecularly heterogeneous disease deriving from post-germinal centre cells or from naïve B-cells undergoing preterminal differentiation. Interestingly, one of the cases bearing somatic hypermutation, also showed Bcl-6 gene mutation, thus further indicating its origin from postgerminal centre cells.

Two different studies reported single cases showing a concomitant IgH and T-cell receptor gene rearrangement. Interestingly, one of these cases also showed immunoreactivity for the T-cell-associated marker CD4 (Tzankov *et al*, 2005; Arbiser *et al*, 2006).

It has been suggested that aberration of genes involved in cell cycle control may contribute to PBL tumourigenesis. In particular, monoallelic deletion of the p53 gene has been reported in 11 of 13 (85%) DLBCL with plasmablastic and or plasmacytoid features analysed, and correlated with a more aggressive clinical course. Hypermethylation of the p16 gene, and a IgH/Myc translocation have been reported in sporadic cases (Arbiser *et al*, 2006; Dawson *et al*, 2007).

Differential diagnosis

Clinical and microscopic features may not be sufficient for distinguishing PBL from other malignancies commonly arising in the oral cavity, such as poorly differentiated carcinoma, malignant melanoma and other types of lymphoproliferative diseases. Poorly differentiated carcinoma may be differentiated from PBL based on its consistent immunoreactivity for cytokeratins and/or epithelial membrane antigen (EMA). Malignant melanoma can be ruled out by using specific melanoma-associated antigens, such as S-100 protein, HMB45 and Melan A (MART-1). Extensive immunoreactivity for CD20 is useful in distinguishing PBL, which is almost invariably negative, from other types of aggressive B-cell lymphomas, which are consistently positive. The distinction between PBL and poorly differentiated myeloma is based mostly on clinical correlations (e.g. the presence of serum monoclonal proteins and/or bone involvement with radiographically evident lesions), as both have similar morphological and phenotypic features.

Concluding remarks

Plasmablastic lymphoma is a distinct type of NHL, that most frequently affects the oral tissue of HIV-positive patients and that usually behaves very aggressively. Both its clinical and histopathological features are frequently ambiguous, thus rendering the correct diagnosis quite difficult in the absence of an exhaustive integration of clinical, morphological, phenotypic and molecular features.

The diagnosis of such neoplasm might be even more challenging in the setting of extra-oral localisations and in immunocompetent patients.

Author contributions

Dr Rafaniello Raviele was responsible for the literature review and writing of the first draft, Dr Pruneri reviewed the morphological, immunophenotypic and molecular data, Professor Maiorano was responsible for the general plan of the paper and for its final version.

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