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SHORT COMMUNICATION

Perivascular inflammatory cells in ovine Visna/maedi encephalitis and their possible role in virus infection and lesion progression

Laura Polledo · Jorge González · Julio Benavides · Beatriz Martínez-Fernández · Mª Carmen Ferreras · Juan F. García Marín

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Abstract We examined the distribution in the perivascular spaces of Visna/maedi antigen, T cells (CD3+, CD4+ and CD8+), B cells and macrophages by immunohistochemistry in 22 natural cases of Visna/maedi encephalitis. Sheep showed *lymphocytic* or *histiocytic* lesions. In mild lymphocytic lesions, the viral antigen was detected in perivascular cuffs where CD8+ T cells predominated, but in severe lymphocytic lesions, sparse antigen was identified, and CD8+/CD4+ T cells appeared in a similar proportion in multilayer perivascular sleeves. In histiocytic lesions, vessels were surrounded by macrophages with abundant viral antigen, with CD8+/CD4+ T cells and B cells in the periphery. These results could reflect different stages of virus neuroinvasion and clarify the neuropathogenesis of Visna/maedi encephalitis.

Keywords Maedi · Visna · Sheep · Encephalitis · Neuropathology · Immunology

Introduction

Visna/maedi virus (VMV) is a lentivirus of the *Retroviridae* family which is related to human immunodeficiency virus (HIV-1) (Thormar 2005) and causes a slow, progressive multi-systemic disease in sheep. Visna/maedi disease (VM) is mainly characterised by chronic inflammation of the lungs, central nervous system (CNS), mammary glands and joints (Cutlip et al. 1988; Dawson 1987). The disease is most commonly presented in respiratory and mammary forms, while the neurological form has often been sporadic (Benavides et al. 2006a, 2009; Lujan et al. 1991; Sigurdsson et al. 1957). The main histologic changes are interstitial inflammation of the lungs and mammary glands with proliferation of lymphoid tissue, as well as non-purulent encephalitis and demyelination of the CNS, including the spinal cord (Benavides et al. 2009; Georgsson et al. 1976; Lujan et al. 1991; Sigurdsson et al. 1957).

In the region of Castilla y León (Spain), VM is considered a widespread disease, with a prevalence estimated at 77 %, especially in the Assaf dairy flocks subjected to an intensive farming setup (Leginagoikoa et al. 2006). In this region, a previous study showed that a proportion as high as 11. 2 % of the sheep showing nervous clinical signs were suffering from the VM (Benavides et al. 2009, 2006c; Gómez et al. 1999). Nervous clinical signs often include progressive ataxia, limb weakness and paresis, particularly in the hind limbs, usually leading to total paralysis and recumbency although the animal remains alert (Benavides et al. 2006c; Christodoulopoulos 2006; Polledo et al. 2011; Sigurdsson et al. 1957). The primary lesion in the brain or spinal cord is a non-suppurative encephalitis predominately periventricular and paraventricular, accompanied or not by non-suppurative choroiditis and meningitis (Benavides et al. 2009; Polledo et al. 2011; Sigurdsson et al. 1957).

The immune response against VMV seems to play a major role in the pathogenetic mechanism; thus, an imbalance in the immune response, whether excessive or deficient, would result in lesion development (Blacklaws 2012; Polledo et al. 2011; Torsteinsdottir et al. 2007, 1992). Once in the host, the main targets of VMV are monocytes/macrophages and dendritic cells, which carry the viral DNA in blood with minimum transcription until the monocytes mature into macrophages in the tissue of affected organs

L. Polledo (✉) · J. González · J. Benavides · B. Martínez-Fernández · M. C. Ferreras · J. F. G. Marín
Pathological Anatomy Section, Animal Health Department, Veterinary School, University of León, 24007, León, Spain
e-mail: lpolr@unileon.es

("Trojan horse" mechanism) (Peluso et al. 1985). It appears that the entry of VMV into the CNS may damage the blood–brain barrier (BBB), leading to changes in vascular permeability and increasing migration of inflammatory cells (lymphocytes and monocytes) to the CNS with secretion of cytokines, creating a vicious circle (Craig et al. 1997; Ebrahimi et al. 2000; Georgsson 1994; Georgsson et al. 1976; Torsteinsdottir et al. 2007). However, this pathological mechanism is not yet fully understood.

A previous study has shown that one sheep with VM nervous lesion showed changes characterised by a diffuse inflammatory infiltrate in the neuroparenchyma with a CD4/CD8 ratio of 0.8 and in the perivascular spaces composed of lymphocytes with a CD4+/CD8+ ratio of 1/3 and 10 % monocytes (Torsteinsdottir et al. 1992), similar to other lentiviruses (CAEV, FIV and HIV-1) (Georgsson 1994). Recently, two main patterns of lesion have been described in relation to each animal: a *lymphocytic type*, where areas of mild–moderate injury characterised by a clear predominance of T cells, mainly CD8+ lymphocytes, are observed, and a *histiocytic type*, characterised by more severe lesions with clear predominance of macrophages, many of them with foamy cytoplasm, mixed with B cells, that is usually accompanied by intense vacuolation foci that coalesce, forming extensive malacic areas.

These lesion patterns could be related to different stages or mechanisms of resistance to the disease. Thus, the lymphocytic lesions could represent some sort of natural resistance to the infection where initial or latent phases are included, and the histiocytic pattern may be the result of an individual poor immune response or greater virulence of the viral strain (Polledo et al. 2011). In this study, we investigated the immunophenotype and distribution of the inflammatory cells specifically within the vascular spaces in relation to the viral antigen and the different patterns of lesion, for the purpose of studying the role of the perivascular spaces in virus neuroinvasion and in the development of the neuroparenchymal lesions (histiocytic or lymphocytic lesions).

Brain tissue samples from natural cases of Visna/maedi encephalitis in 22 adult sheep (over 2 years old) of the Spanish Assaf breed were examined. All of them were naturally infected cases which had been submitted to the Pathology Diagnosis Service of the Veterinary School of León with nervous clinical signs and had been diagnosed as VM infected. CNS tissue samples were obtained systematically, taking different sections: cortex, diencephalon, corpus callosum, hippocampus, midbrain, cerebellar cortex, pons and cerebellar peduncles, medulla oblongata, and cervical, thoracic and lumbar spinal cord. Sample tissues were fixed in 10 % buffered formalin, stained with haematoxylin–eosin and examined by light microscopy. Samples from these same locations were fixed in zinc salt fixative (0.5 % zinc chloride, 0.5 % zinc acetate in 0.05 % Tris buffer, 0.1 M calcium acetate, pH=7.4) and tested using immunohistochemical techniques (IHC) using serial tissue sections. These serial tissue sections were stained with primary antibodies raised against the p27 VM viral antigen (Gelmetti et al. 2000), as previously described (Benavides et al. 2006b), and T cells (CD3+, CD4+ and CD8+), B cells (CD79 αcy) and macrophages (CD68), using previously described IHC staining procedures (Polledo et al. 2011). Samples from a sheep without characteristic lesions of VM which showed negative results to PCR procedures and serology were used as negative control. A semiquantitative analysis of the presence of the different cell immunophenotypes in perivascular cuffs associated with the inflammatory response to VM antigen was carried out.

Serum samples were obtained from the 22 sheep to evaluate the presence of antibodies against VMV using a commercial test (Elitest®, Hyphen BioMed, Neuville/Oise, France), following the manufacturer's instructions. ELISA results were reported as positive or negative on the basis of the cutoff value calculated following the manufacturer's instructions (absorbance, 450 nm).

Histological examination revealed that all the 22 studied sheep presented characteristic CNS lesions of VM encephalitis, 9 sheep showed lymphocytic lesions and 13 sheep showed histiocytic lesions. Five sheep that showed mild nervous signs (lethargy, tremors, incoordination or mild ataxia of the hind limbs) presented non-suppurative lymphocytic encephalitis consisting only in perivascular cuffs spread throughout the neuroparenchyma, characterised by the arrangement of round cells in mono- or multiple layers around blood vessels with no or sparse infiltration of the neuropil, named *mild lymphocytic lesions* in this study. Another four sheep with more severe nervous clinical signs (progressive ataxia and recumbency) showed these similar mono- and multilayer perivascular cuffs accompanied by a lymphocytic infiltrate in the neuroparenchyma, and these were considered *severe lymphocytic lesions*. Thirteen animals showed histiocytic lesions with extensive areas of malacia and a non-suppurative histiocytic infiltrate with evident predominance of large and foamy macrophages. These 13 sheep with histiocytic encephalitis also showed severe nervous signs of progressive ataxia and recumbency, but five of them with more than 2 weeks of recumbency. The 22 sheep yielded positive results to the serological tests.

VMV antigen was detected in the brain tissue sections of all the animals in this study, while the control sections were negative. The positive signal was found predominantly in the cytoplasm of the macrophages/microglia located in the CNS lesions. The result of the analysis of the distribution of the viral antigen and the different perivascular cell types associated with the inflammatory response to VMV infection is detailed in Table 1. These results showed clear

Table 1 Visna/maedi antigen distribution and cell immunophenotypes forming the perivascular cuff layers

	Mild lesion		Lymphocytic lesion		Histiocytic lesion	
PC	Monolayer	Multilayer	Monolayer	Multilayer	Monolayer	Multilayer
VM antigen	++	++	S	S	+	+
T cell CD3+	+++	+++	+++	+++	+	++
T cell CD8+	+++	++	+++	++	+	++
T cell CD4+	+	++	+	++	+	++
Macrophage	+	+	+	+	+++	++
B cells	S	S	S	S	+	++

Results of semiquantitative analysis of viral antigen and the cell immunophenotypes in perivascular spaces of mild, lymphocytic and histiocytic lesions, scored as s, sporadic; +, few; ++, moderate, and +++, many

PC Perivascular cuffs formed by cellular mono- or multiple layers

differences in the phenotypical cellular composition in perivascular spaces in various types of lesion and in the distribution of the VM antigen.

In mild lymphocytic lesions, where perivascular cuffs seemed to be the only damage, with scarce inflammatory response in the neuropil, VM antigen immunoreactivity was detected in these perivascular sleeves. The antigen-positive signal was found in the cytoplasm of macrophage-like cells close to the endothelium, and mixed between the cellular sleeves, but it was hardly detected in the neuroparenchyma (Fig. 1). Interestingly, this finding has been observed in this type of lesion alone, so this antigen immunolabelling could correspond to infected perivascular macrophages, or circulating infected monocytes that differentiate into macrophages entering the CNS by this route and allowing viral replication. These observations would confirm the previously proposed models of VMV neuroinvasion, based on the "Trojan horse" pathological mechanism (Georgsson et al. 1989; Peluso et al. 1985). In this way, in other lentivirus infections such as simian immunodeficiency virus (SIV) and HIV-1, it has been demonstrated that perivascular macrophages are the primary cells productively infected by the virus, resulting in a disruption of the BBB and allowing greater entry of infected cells into the CNS (Kim et al. 2003; Persidsky, 1999; Strazza et al. 2011; Williams et al. 2001b), as could initially occur in VM encephalitis. Thus, most cells (over 90 %) which made up these perivascular sleeves were T cells mixed with scattered macrophages, often close to the endothelium. Specifically, the CD8+ T cell subpopulation clearly predominated over CD4+ T lymphocytes in the mono/bilayer perivascular cuffs, but larger multilayer perivascular cuffs showed these cells in similar proportions of 50 %. B cells were only sporadically observed. Thus, it is possible that in mild VM encephalitis, the CD8+ lymphocytes located around blood vessels may be cytotoxic effector cells when they encounter cells presenting viral antigen. Likewise, in SIV encephalitis, it has been reported that CD8+ lymphocytes located angiocentrically appear to control the accumulation of infected macrophages in the CNS in an antigenic-specific manner, also with little accumulation of CD4+ lymphocytes (Freel et al. 2011; Kim et al. 2004). Specifically, this feature has been demonstrated in SIV infection when the viral load was increased, and progression of the disease was accelerated, in animals whose CD8+ T cells were depleted (Schmitz et al. 1999; Williams et al. 2001a). However, it has previously been suggested that the

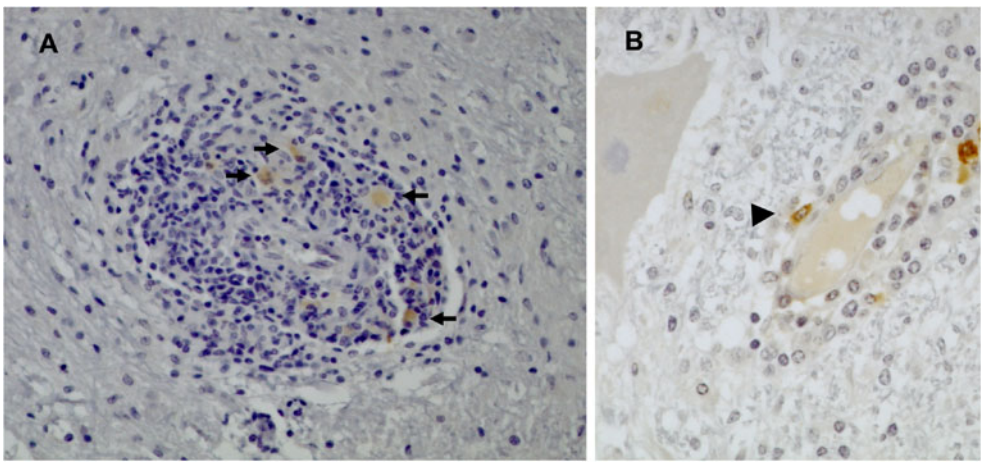

Fig. 1 Cerebellar peduncles (**a**) and mild lymphocytic lesion (**b**) of VM encephalitis essentially composed of perivascular cuffs with positive antigen signal in macrophage-like cells mixed between the cellular sleeves (*arrows*). Note that in **b** the antigen is located close to the endothelium (*arrowhead*). Anti-p27 VM antigen IHC. **a** ×150, **b** ×250

cellular immune response of CD8+ together with CD4+ T lymphocytes in inflammatory lesions of VM may be directed not only against the virus but also against self-antigen (Blacklaws 2012; Torsteinsdottir et al. 2007, 1992), so the presence of CD4+ T cells together with CD8+ T cells in multilayer perivascular cuffs detected in this study could be representing a stage of lesion progression to more severe lymphocytic lesions.

In CNS lesions with a more severe lymphocytic infiltrate of the neuroparenchyma (*severe lymphocytic lesions*) with CD8+ lymphocyte predominance, the presence of antigenic positive signal was very sparse in the perivascular spaces and the neuropil (Fig. 2). Cell immunophenotypes which formed both mono/bilayer and multilayer perivascular cuffs were very similar to the ones previously described in mild lymphocytic lesions, but with a greater abundance of multilayer perivascular sleeves. In severe lymphocytic lesions, despite the possible role of the CD8+ T cells in the control of viral replication, this vascular lymphocytic inflammatory response could also cause tissue damage due to dysregulation of the immune response. In this way, in SIV encephalitis lesions, it has also been reported that a large number of activated CD8+ T lymphocytes accumulate abnormally in the brain, resulting in increased concentrations of cytokines to pathological levels (Marcondes et al. 2001). Thus, the presence of this lymphocytic infiltrate may be essential in controlling the infection, although it may also contribute to the progression of the VM lesion. In these perivascular spaces, the number of B cells was very low, so this feature indicates that the humoral immune response would be minimal in this type of lesion, with cellular immunity playing the major role.

In particular, examination of lesions in the CNS with histiocytic infiltration revealed a high number of VMV-positive cells in the central areas of the lesion, mixed with malacia (Fig. 3), but this antigen-positive signal was rarely detected immediately adjacent to the endothelium or in perivascular cuffs. In these histiocytic infiltrates, macrophages with a clear cytoplasm ("gitter cells") clearly predominated over other cells such as CD8+ and CD4+ T cells and B cells. These observations would support the hypothesis of development of VM encephalitis after neuroinvasion of the CNS. Thus, once in the tissue, infected monocytes mature and allow viral replication and recruitment of more infected cells, based on an immune activation in response to viral antigen that also causes inflammatory infiltration and damage of the CNS tissue (Blacklaws 2012; Torsteinsdottir et al. 2007). This pathological model would explain the abundance of macrophages and viral antigen seen in the parenchyma in the histiocytic lesion. This way, a slow rate of VM neutralization by antibodies relative to the rate of virus adsorption to the cell surface has been suggested as a possible mechanism whereby the virus can spread from cell to cell in the presence of neutralizing antibodies with no free virus release (Thormar 2005). This feature could explain the persistence and replication of virus in the neuroparenchyma of the histiocytic lesion in the face of an active immune response. Likewise, the viral induction of apoptosis has been proposed as the major mechanism of cell death occurring during MVV infection (Duval et al. 2002a), and this mechanism is considered to promote cell-to-cell spreading, virus release and stimulation of the immune response (Duval et al. 2002b).

The IHC study of vascular spaces in the areas with abundant malacia of the histiocytic lesions, often central areas, showed that some blood vessels were completely surrounded by the macrophage infiltration, with few B cells and T cells (mainly CD8+ lymphocytes, with CD4+ in lower proportions) adjacent to the endothelium that

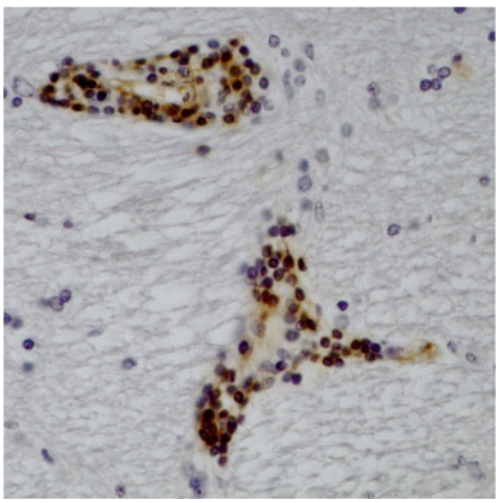

Fig. 2 Cerebellar peduncles, mononuclear cells around blood vessels in lymphocytic lesions of VM encephalitis, with clear predominance of CD8+ T cell immunoreactivity. Anti-CD8+ T cell IHC. ×250

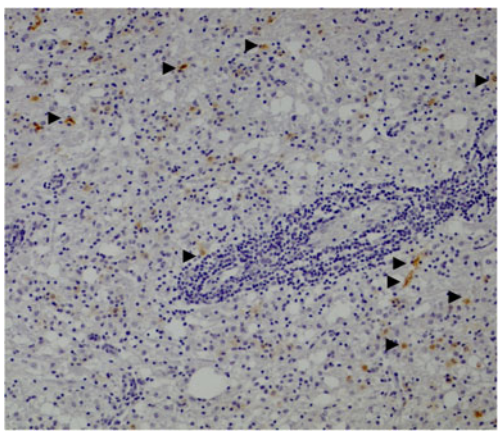

Fig. 3 Cerebellar peduncles, histiocytic inflammatory demyelination lesion of VM encephalitis. Antigen-positive signal (*arrowheads*) located in the malacic area. Anti-p27 VM antigen IHC ×100

was occasionally disrupted. In the periphery of the lesion, where multilayer perivascular cuffs were often located, the layers close to the endothelium were mainly formed by T cells (CD8+ and CD4+, in similar proportions) with around 20 % of B cells, and macrophages behind these layers. This lymphocytic perivascular cuffs may provide a cellular immune response similar to the one described for lymphocytic lesions in response to the spread of the lesion and the consequent endothelial damage. In addition, the observed CD4+ T cells together with B cells tightly packed in these perivascular cuffs may produce an effective utilisation of CD4+ lymphocytic cytokines by B cells, resulting in strong antibody production (Esiri and Gay, 1990) that may be directed not only against the virus, but also against self-antigens although this is still not clear (Panitch et al. 1976; Torsteinsdottir et al. 2007). Thus, in these histiocytic lesions, a non-effective humoral immune response may be involved in the development of tissue damage.

To summarize, this study reinforces and clarifies the prior model of development of VM encephalitis (Blacklaws 2012; Polledo et al. 2011; Torsteinsdottir et al. 2007). Thus, the detection of viral antigen in the perivascular spaces, but not in the neuropil, in the described mild lymphocytic lesions may reflect viral neuroinvasion through the infection of perivascular macrophages or through the entry of infected monocytes into the CNS. Once the infected cells are located in the CNS, viral replication could be controlled by an effective lymphocytic cellular response, but could also progress to severe encephalitis due to dysregulation of the immune response. In the case of lesion progression, immune activation would induce the recruitment and differentiation of more monocytes to macrophages which would enable continuous viral replication and production of cytokines, with an additional non-effective humoral immune response resulting in a severe histiocytic infiltration and lesion of the CNS. This study showed a spectrum of lesions and immunopathological response closely related to the cells and antigen observed in perivascular spaces, and also a possible relation between the spreading of the virus in the neuroparenchyma and the type and severity of the lesion.

However, the material examined in this study was taken from natural cases of ovine VM with varying degrees of severity which had already shown nervous clinical signs, so further understanding of the inflammatory process in VM encephalitis will require analysis of the inflammatory cells as well as expression of cytokines and endothelial adhesion molecules at well-established stages of the disease, including animals in the subclinical phase.

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