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CD1a reactivity in non-neoplastic adenohypophysis

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Abstract

Within the differential diagnosis of patients presenting with sellar or suprasellar lesions is Langerhans cell histiocytosis (LCH). CD1a staining is frequently used to identify the presence of an abnormal proliferation of Langerhans cells on histological sections and contributes to the diagnosis of LCH. Here, we report that the MTB-1 monoclonal antibody against the CD1a antigen reacts to native adenohypophyseal epithelial cells. We show that immunohistochemistry for CD1a exhibits strong positivity in all autopsy and surgically resected non-neoplastic adenohypophysis tested. Thus, CD1a positivity by itself should be interpreted with caution, and we recommend the routine use of a panel of stains including CD1a, Langerin, and synaptophysin in conjunction with morphological analysis before a diagnosis of LCH is rendered. In addition, we find that pituitary adenomas fail to stain for CD1a prompting consideration of the utility of this stain as a marker for non-neoplastic gland.

Keywords

CD1a; adenohypophysis; pituitary adenoma; Langerhans histiocytosis

Introduction

Mass lesions of the pituitary region include a variety of neoplastic and non-neoplastic entities. Neoplasms that may present in this region include pituitary adenoma, craniopharyngioma, germ cell tumors, pituicytoma, granular cell tumors, meningioma, lymphoma and Langerhans histiocytosis (LCH) ¹. Hypophysitis, which may be primary or secondary (e.g. to infection) and may also present as a mass lesion, is categorized as lymphocytic, granulomatous, xanthomatous and necrotizing based on histopathology ². Hypophysitis associated with IgG4-positive plasma cells has also been described ^{3,4}. In evaluating a pituitary mass lesion that reveals histologic evidence of a robust inflammatory component, LCH should enter into the differential diagnosis. Commonly used antibodies to

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Conflict of Interest:

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highlight the presence of Langerhans cells includes those binding to CD1a and langerin antigens ⁵.

CD1a is a surface glycoprotein that is known to be expressed in cortical thymocytes as well as Langerhans cells and other dendritic cell subsets ⁶. More recently, CD1a expression has also been detected in mature, polyclonal T cells ⁷. Immunohistochemical staining for this protein has also been reported in gastrointestinal epithelial cells in the context of Barrett's metaplasia ^{8,9}.

The case that prompted us to survey the immunohistochemical pattern of CD1a staining in the pituitary gland was that of an 11-year-old girl who presented with headache and diabetes insipidus. Imaging of the sellar region revealed a contrast enhancing cystic mass with a differential diagnosis including germ cell tumor, craniopharyngioma, LCH, and pituitary adenoma. Histopathological analysis of the lesion showed a robust inflammatory infiltrate comprising plasma cells, eosinophils, and mature appearing lymphocytes involving non-neoplastic adenohypophysis (Figure 1A). CD1a immunohistochemical staining highlighted clusters of strongly staining cells (Figure 1B) and a diagnosis of Langerhans histiocytosis was initially rendered. Further examination revealed that the CD1a-immunoreactive cells co-localized with native adenohypophyseal epithelial cells, which were also positive for synaptophysin (Figure 1C) and negative for Langerin (Figure 1D). Additionally, IgG4-immunoreactive plasma cells were dispersed throughout the lesion as were rare ciliated epithelial cells (data not shown). The final conclusion was that the lesion represented a non-neoplastic inflammatory process with a differential diagnosis including lymphocytic hypophysitis, IgG4-associated hypophysitis, or a robust inflammatory response in the setting of rupture of a benign cystic lesion such as Rathke cleft cyst. Given the markedly different post-surgical clinical management strategies and sequelae for patients with LCH versus other neoplastic and inflammatory processes ^{10,11}, misinterpreted CD1a immunohistochemical staining within pituitary lesions represents a diagnostic pitfall with important clinical ramifications. We therefore examined further the staining properties of CD1a across a series of pituitary specimens.

Materials and Methods

Formalin fixed paraffin embedded samples of pituitary tissue regions were examined (n=23 specimens from 17 unique patients). These samples included surgically resected pituitary adenoma (n=9, including 1 prolactinoma, 2 adenomas with evidence of ACTH expression, and 6 adenomas without significant hormonal expression); non-neoplastic surgically resected pituitary tissue (n=7); as well as pituitary gland tissue obtained at autopsy (n=7). All samples underwent immunohistochemistry for CD1a. The antibody used was the MTB-1 mouse monoclonal raised against a recombinant fusion protein corresponding to the full external domain of the human CD1a molecule (Leica's Bond™ Ready-To-Use antibody; catalog no PA0235). According to the manufacturer, the antibody is specific to CD1a with possible cross-reactivity to CD1b.

An automated Leica Bond-III stainer was used to perform the immunohistochemistry with antigen retrieval protocol H2-20. Tissue samples were scored as positive when definitive

epithelial immunoreactivity was observed. Samples were scored as negative if all cells were negative or if only rare isolated cells showed immunoreactivity and did not display epithelial morphology. In samples with heterogeneous regions, such as specimens with mixed pituitary adenoma and non-neoplastic pituitary gland, staining was correlated with hematoxylin and eosin (H&E), reticulin staining, and/or other immunohistochemical stains including synaptophysin and pituitary hormone markers that had been conducted at the time of clinical workup, to distinguish these components, which were then scored separately. In addition, a subset of samples (n = 8; 4 each of autopsy and adenoma samples) were additionally stained with a second monoclonal antibody (Ventana's Ready to Use antibody, Clone EP3622; antigen retrieval: CC1).

Results

To assess CD1a immunoreactivity in pituitary specimens, we surveyed 9 surgically resected pituitary adenoma specimens (6 of which additionally contained non-neoplastic adenohypophysis), one case of surgically resected pituitary tissue not associated with pituitary adenoma, as well as 7 additional non-neoplastic pituitary glands obtained at autopsy (Table 1). Remarkably, all non-neoplastic adenohypophyseal tissue specimens harbored epithelial cells clearly labeled with CD1a antibody while none of the adenomatous tissue showed positive staining of epithelial cells. Indeed, in some cases harboring regions of both pituitary adenoma and non-neoplastic adenohypophysis, CD1a staining permitted independent demarcation of these areas (Figure 2). For example, areas that showed morphological features, reticulin staining, and hormone expression pattern consistent with non-neoplastic gland were positive for CD1a in resection specimens also containing prolactinoma (Figure 2E) as well as a null-cell adenoma (Figure 2G), while areas consistent with adenoma were negative for CD1a (Figure 2E and 2J). 3 of 9 adenoma cases showed very rare isolated cells with CD1a immunoreactivity and these specimens were interpreted as negative, with no epithelial immunoreactivity seen. These cells may have represented rare CD1a-positive immune cells. Occasional isolated cells positive for Langerin were also observed, but did not appear epithelial and were not clustered (Figure 1D). We did not observe a correlation between CD1a staining and S100, GFAP, or any of the 6 major hormones found within non-neoplastic adenohypophysis (Figures 3 and 4). Finally, of the 8 samples stained using an alternative monoclonal antibody against CD1a (clone EP3622), only one case of a pituitary adenoma showed focal strong staining (Figure SF1-A); this adenoma was completely negative using the MTB-1 clone (Figure SF1-B) and did not exhibit immunohistochemical expression of pituitary hormones. Using the EP3622 clone, we observed a only faint blush within some foci of autopsy samples (Figure SF1-C) and negligible staining in non-neoplastic tissue within surgical resection specimens (Figure SF1-E) as compared to strong staining seen using the MTB-1 clone (Figure SF1-D,F).

Discussion

In evaluating surgically resected specimens from the sellar region, antibodies to CD1a are commonly employed when a diagnosis of LCH is considered. Adding to prior reports of CD1a-immunoreactivity in gastrointestinal epithelial cells ^{8,9}, here we have demonstrated immunohistochemical reactivity of a CD1a antibody with another epithelial cell type,

glandular cells of the adenohypophysis. Specifically, the monoclonal MTB-1 antibody reacts with non-neoplastic adenohypophyseal epithelial cells, and is negative in neoplastic epithelial cells in the pituitary adenomas we have tested. We did not observe similar immunoreactivity using an antibody recognizing langerin, where only isolated rare cells showed immunoreactivity.

Whether or not the CD1a protein itself is expressed within these cells or whether the antibody cross reacts with a different protein found within pituitary tissue requires further study. The absence of a similar staining pattern using an alternative clone to CD1a argues against bona fide CD1a expression within neuroendocrine cells of the pituitary. Whether or not the MTB-1 clone in particular is cross reacting to an antigen that is specific to non-neoplastic neuroendocrine cells remains an intriguing question. We did not observe a distinct correlation with MTB-1 staining and staining for any of the 6 major adenohypophyseal hormones.

Pathologists should be aware that in the context of pituitary lesions with marked inflammation, epithelial cells may react with CD1a antibodies, particularly with the MTB1 monoclonal antibody and give the false impression of a dense proliferation of Langerhans cells. Careful correlation of the immunohistochemical pattern with the original H&E-stained section as well as additional markers such as synaptophysin for neuroendocrine cells and langerin for Langerhans cells should be evaluated prior to settling on a diagnosis of LCH. These findings have the potential to prevent diagnostic errors and ensuing therapeutic mismanagement for patients presenting with pituitary masses.

Finally, given our evidence that the MTB-1 monoclonal antibody against CD1a is consistently negative in pituitary adenoma, there is potential for use of this antibody in distinguishing neoplastic from non-neoplastic adenohypophyseal lesions as an adjunct to reticulin staining and other immunohistochemical stains, particularly in small samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Prominent CD1a reactivity in adenohypophyseal epithelial cells

The lesion, comprising an exuberant mixed inflammatory infiltrate with plasma cells and eosinophils, focally involved non-neoplastic pituitary gland (A). Numerous CD1a-positive cells were seen (B) and a diagnosis of LCH was rendered. Closer inspection revealed that the CD1a-positive cells co-localized with native adenohypophyseal epithelial cells that were also synaptophysin positive (C) and negative for langerin (D). Scale bars = 50um.

Figure 2. CD1a staining is present in non-neoplastic adenohypophysis

Prolactinoma at the interface with normal adjacent pituitary gland highlighting absence of CD1a staining in the adenoma and CD1a-positivity in the non-neoplastic gland (A–E). A second case showing non-neoplastic gland (upper left) and adenoma (lower right) (F). A third example of non-neoplastic gland within an adenoma resection specimen (G–I) as compared to adenoma in the same specimen (J–L). Scale bars = 50um.

Figure 3. CD1a stains neuroendocrine epithelial cells, not folliculostellate cells

CD1a staining using the MTB-1 clone of non-neoplastic pituitary gland shows numerous strongly staining cells (A) the density and pattern of which indicates that a subset of synaptophysin-positive neuroendocrine cells (B) are also positive for CD1a. In contrast, there is no correlation between GFAP (C) and S100 staining (D) with CD1a staining. Hematoxylin and eosin staining is shown for histological reference (E). Scale bars = 100um.

Figure 4. CD1a staining does not correlate with adenohypophyseal hormones

H&E staining at the interface between non-neoplastic pituitary gland and a prolactin-producing adenoma (A). Synaptophysin staining (B) in conjunction with CD1a staining (C) show that a subset of neuroendocrine epithelial cells within non-neoplastic gland are positive for CD1a. Staining for prolactin (D), adrenocorticotrophic hormone (E), thyroid stimulating hormone (F), human growth hormone (G), luteinizing hormone (H), and follicle stimulating hormone (I) does not show correlation with CD1a staining. Scale bars = 50 μ m.

Table 1
CD1a staining of adenohypophysis

For surgically resected specimens (S), “non-neoplastic” indicates non-neoplastic adenohypophysis present within the surgically resected tissue. “A” indicates autopsy tissue.

CASE	DESCRIPTION	RESULT
S-1	ADENOMA	NEG
S-3	ADENOMA	NEG
S-4	ADENOMA	NEG
S-5	ADENOMA	NEG
S-6	ADENOMA	NEG
S-7	ADENOMA	NEG
S-8	ADENOMA	NEG
S-9	ADENOMA	NEG
S-10	ADENOMA	NEG
A-1	AUTOPSY	POS
A-2	AUTOPSY	POS
A-3	AUTOPSY	POS
A-4	AUTOPSY	POS
A-5	AUTOPSY	POS
A-6	AUTOPSY	POS
A-7	AUTOPSY	POS
S-1	NON-NEOPLASTIC	POS
S-2	NON-NEOPLASTIC	POS
S-3	NON-NEOPLASTIC	POS
S-4	NON-NEOPLASTIC	POS
S-5	NON-NEOPLASTIC	POS
S-6	NON-NEOPLASTIC	POS
S-9	NON-NEOPLASTIC	POS