Immunoglobulin heavy chain patterns in reactive lymphadenopathy

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Abstract

Thirty one lymph nodes taken from 24 benign reactive cases, three cases of angiolymphoid hyperplasia with eosinophilia, one case of Kimura's disease and three cases of Hodgkin's disease, were stained for immunoglobulin heavy chains IgG, IgM, IgA and IgE using the peroxidase-antiperoxidase method. Reticular staining of germinal centres and cells containing immunoglobulin in germinal centres and extrafollicular regions were features of all groups. No staining pattern was diagnostic for any of these conditions and in particular, the reticular staining pattern of IgE in the germinal centres that is frequently reported in Kimura's disease and in angiolymphoid hyperplasia with eosinophilia was non-specific.

A reticular pattern of IgE staining in the germinal centres of lymph nodes in Kimura's disease was shown using immunofluorescence.¹ Other studies have confirmed this observation.²⁻⁴ A similar finding was also noted in the subcutaneous lymphoid follicles of angiolymphoid hyperplasia with eosinophilia (ALHE).⁵⁻⁸

The frequent documentation of this feature in these two conditions and the controversy surrounding their association has created the impression of their IgE specificity. We decided to assess this and other staining patterns of immunoglobulin heavy chains in reactive lymph nodes with two purposes in mind. Firstly, to determine if IgE specificity in ALHE and Kimura's disease would throw an interesting light on the theory that these are

not necessarily two separate entities, and secondly to see if there was any pattern of heavy chain staining found more frequently in a specific reactive condition.

Methods

Slides stained with haematoxylin and eosin of 24 cases of reactive lymph nodes were selected from the histopathology files of the Hammersmith Hospital on the basis of the presence of prominent reactive germinal centres. Specific diagnoses are shown in the table. Three cases of ALHE, one of Kimura's disease, and three of Hodgkin's disease, all with prominent germinal centres, were also selected. The lymph nodes were from the cervical area in most cases. Exceptions included two cases of human immunodeficiency virus (HIV) lymphadenopathy in lymph nodes in the parotid gland, and the ALHE cases, which involved subcutaneous tissue in the deltoid region. The five cases of angiofollicular hyperplasia included in the study were of the plasma cell variety and all had a polytypic plasma cell population. The stained sections were all reviewed by MS and ABA and the specific diagnoses confirmed. Formalin fixed, paraffin wax embedded sections were stained using the peroxidase-antiperoxidase method for IgG, IgM, IgA and IgE (antibodies to IgG, IgM, IgA were from Dako Ltd and IgE was from Hoechst). IgE specificity was assessed by its staining of mast cells.

Results

Two basic staining patterns were noted with all the immunoglobulin heavy chains: (1) germinal centre reticular staining (fig 1); (2) cells

Immunoglobulin heavy chain patterns (numbers of cases showing positive staining)

	Germinal centre reticular pattern				Ig containing cells			
	IgE	IgG	IgM	IgA	IgE	IgG	IgM	IgA
Benign reactive conditions:								
Non-specific n = 10	3	5	10	6	9	9	10	10
Dermatopathic lymphadenopathy n = 2	2	1	2	2	2	2	2	2
Angiofollicular lymphadenopathy n = 5	1	5	3	2	5	5	5	5
SLE n = 2	2	2	2	1	2	2	2	2
Rheumatoid arthritis n = 2	2	2	2	2	2	2	2	2
Tuberculosis n = 1	1	0	1	0	1	1	1	1
*HIV n = 2	2	0	0	0	2	2	2	2
Total n = 24	13	15	20	13	23	23	24	24
ALHE/Kimura's disease:								
ALHE n = 3	3	2	3	1	3	3	3	3
Kimura's n = 1	1	0	1	0	1	1	1	1
Total n = 4	4	2	4	1	4	4	4	4
Hodgkin's disease n = 3	2	0	2	0	3	3	3	3
Total n = 3	2	0	2	0	3	3	3	3

SLE = Systemic lupus erythematosus; * = HIV related lymphadenopathy.

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Figure 1 Reticular pattern within a germinal centre on staining for IgE in a reactive lymph node (immunoperoxidase stain with silver enhancement and haematoxylin counterstain).

containing immunoglobulin in the germinal centres and in the extrafollicular region.

For comparative purposes the diagnostic entities were subdivided into three groups: (1) benign reactive conditions ($n = 24$); (2) ALHE/Kimura's disease ($n = 4$); and (3) Hodgkin's disease ($n = 3$).

Of the 24 cases of reactive conditions, 13 showed a reticular staining pattern for IgE, 15 for IgG, 20 for IgM and 13 for IgA. All the four cases in the ALHE/Kimura's disease group were positive for IgE reticular staining and of the three Hodgkin's disease nodes, two were positive for IgE. While widespread reticular staining for IgE was seen in germinal centres of both cases of HIV related lymphadenopathy (fig 2), no similar staining pattern was seen with the other heavy chains in these cases. Scattered positive cells in germinal centres and extrafollicular plasma cells were noted with all the heavy chains, IgG and IgM being the two most common.

Figure 2 IgE staining of germinal centre in a lymph node from an HIV positive patient: the reticular pattern is destroyed in areas by follicular lysis (arrowheads).

Discussion

Two patterns of immunoglobulin heavy chain staining have been described in this study. Norton and Isaacson,⁹ using a more sensitive technique (modified avidin biotin complex method), showed a membrane staining pattern of lymphocytes in lymph nodes. In pattern 2 the positive cells in the germinal centre were mostly small cleaved cells or centrocytes and those in the extrafollicular region were predominantly plasma cells.

The reticular staining pattern in all reactive nodes was seen with IgG and IgM in more cases than the other heavy chains. IgM staining particularly showed the reticular pattern; heavy IgG staining was noted in extrafollicular plasma cells. This was not specific for any one diagnosis. In the ALHE/Kimura's group IgE and IgM reticular staining predominated and a similar pattern was seen, but to a lesser extent, in the cases of Hodgkin's disease. The fact that staining patterns could not be associated with any one reactive condition presumably suggests that the patterns depend on the duration of the antigenic stimulus and not on the nature of the antigen.

The reticular staining of IgE has been reported only in a single case of angioimmunoblastic lymphadenopathy¹⁰ in addition to the several reports on Kimura's disease and ALHE. In a study of the distribution of IgE forming cells in lymphoid tissue Tada and Ishizaka noted the reticular pattern in the germinal centres of tonsils and adenoids, and sparingly in the paratracheal lymph nodes, using immunofluorescence.¹¹ The cervical and axillary lymph nodes were negative for this staining pattern. IgE positive plasma cells, however, were present in all groups of lymphoid tissue.

Similar reticular staining patterns in germinal centres have been obtained using antibodies to dendritic reticulum cells.¹² These cells have a role in the presentation of antigens to germinal centre B cells and in the generation of memory B cells.¹³ The antigenic profile of dendritic reticulum cells has been studied extensively. These cells are HLA-DR positive and possess receptors for C3 and immunoglobulin, although in most reports IgG, IgM, and IgA are the heavy chains frequently cited.¹²⁻¹⁵ The reticular staining for IgE confirms the presence of Fc receptors to IgE on the dendritic reticulum cells.

The IgE staining in our study was seen in 13 of the 24 reactive lymph nodes including the single case of tuberculosis, two cases of HIV related lymphadenopathy, two of the three cases of Hodgkin's disease and in all the three cases of ALHE and in one case of Kimura's disease. IgE positivity was seen in examples of all the entities examined. It is therefore not specific to ALHE and Kimura's disease. None of the staining patterns identified was specific enough to help in the diagnosis of any of the conditions.

It is interesting to note that in the two cases of HIV related lymphadenopathy germinal centre reticular staining was positive only for IgE; IgG, IgM, and IgA were all negative,

although cells containing immunoglobulin were seen in the germinal centres and the extrafollicular regions.

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- 1 Takenaka T, Okuda M, Usani A, *et al.* Histological and immunological studies on eosinophilic granuloma of soft tissue, so-called Kimura's disease. *Clin Allergy* 1976;6: 27-39.
- 2 Maeda K, Jimbow K. Kimura's disease: immunohistochemistry of infiltrating cells using monoclonal and polyclonal antibodies. *J Dermatol* 1986;13:190-5.
- 3 Kuo T, Shih L, Chan H. Kimura's disease. Involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. *Am J Surg Pathol* 1988; 12:843-54.
- 4 Hui PK, Chan JKC, Ng CS, Kung ITM, Gwi E. Lymphadenopathy of Kimura's disease. *Am J Surg Pathol* 1989; 13:177-86.
- 5 Moesner J, Pallesen R, Sorensen B. Angiolymphoid hyperplasia with eosinophilia (Kimura's disease). *Arch Dermatol* 1981;117:650-3.
- 6 Wright DH, Padley NR, Judd MA. Angiolymphoid hyperplasia with eosinophilia simulating lymphadenopathy. *Histopathology* 1981;5:127-40.
- 7 Hallam LA, Mackinlay GA, Wright AMA. Angiolymphoid hyperplasia with eosinophilia: possible aetiological role for immunisation. *J Clin Pathol* 1989;42:944-9.
- 8 Akosa AB, Ali MH, Khoo CTK, Evans DM. Angiolymphoid hyperplasia with eosinophilia associated with tetanus toxoid vaccination. *Histopathology* 1990;16: 589-93.
- 9 Norton AJ, Isaacson PG. Detailed phenotypic analysis of B cell lymphoma using a panel of antibodies reactive in routinely fixed wax embedded tissue. *Am J Pathol* 1987; 128:225-40.
- 10 Jones DB, Castleden M, Smith JL, Mephan BL, Wright DH. Immunopathology of angioimmunoblastic lymphadenopathy. *Br J Cancer* 1978;37:1053-62.
- 11 Tada T, Ishizaka K. Distribution of IgE forming cells in lymphoid tissues of the human and monkey. *J Immunol* 1970;104:377-81.
- 12 van der Valk P, van der Loo EM, Jansen J, Daha MR, Meijer CJLM. Analysis of lymphoid and dendritic cells in human lymph nodes, tonsil and spleen. *Virchows Arch (Cell Pathol)* 1984;45:169-85.
- 13 Peters JPI, Rademakers LHPM, Roelofs JMM, deJong D, van Unnik JAM. Distribution of dendritic reticulum cells in follicular lymphoma and reactive hyperplasia. *Virchows Arch (Cell Pathol)* 1984;46:215-28.
- 14 Stein H, Gerdes J, Mason DY. The normal and malignant germinal center. *Clin Hematol* 1982;11:531-59.
- 15 Heinen E, Lilet-Leclercq C, Mason DY, *et al.* Isolation of follicular dendritic cells from human tonsils and adenoids. Immunocytochemical characteristics. *Eur J Immunol* 1984;14:267-73.