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Case report

Lymphocyte predominant Hodgkin's disease of nodular subtype combined with pulmonary lymphoid infiltration and hypogammaglobulinaemia *

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Summary. Two cases of lymphocyte predominant Hodgkin's disease of nodular subtype (HDNP) are reported. In contrast to classic cases of HDNP which often involve only one lymph node region and show no further symptoms, these two patients exhibited lymphoid infiltrates of the lung and hypogammaglobulinaemia. In patient 2 a monotypic immunoglobulin pattern (light chain kappa) was demonstrated in the L & H-, Hodgkin- and Sternberg-Reed cells. Both cases represent an uncommon variant of lymphocyte predominant Hodgkin's disease.

Key words: Hypogammaglobulinaemia – Lymphocyte predominant Hodgkin's disease of nodular subtype – Monoclonal L & H cells – Pulmonary lymphoid hyperplasia

Introduction

In contrast to all other types of Hodgkin's disease (HD), lymphocyte predominant Hodgkin's disease of nodular subtype (HDNP) involves the B-cell system primarily. Many findings speak for the B-cell nature of this neoplasm; B-lymphocytes dominate the infiltrates (Burns et al. 1984; Pinkus and Said 1985; Hansmann et al. 1986; Timens et al. 1986; Lennert and Hansmann 1987) the Hodgkin-, Sternberg-Reed- and L & H cells express B-cell markers (Pinkus and Said 1985; Hansmann et al. 1986; Timens et al. 1986) and transformation into high grade B-cell lymphoma is possible (Miettinen et al. 1983; Lennert and Hansmann 1987; Trudel et al. 1987; Sundeen et al. 1988 Hansmann et al. 1989). However, immunohistochemical (Stein et al. 1986; Pinkus and Said 1985; Timens et al. 1986; Sundeen et al. 1988) and molecular genetic methods (Griesser et al. 1987; Griesser and Mak 1988; Sundeen et al. 1988; Linden et al. 1988) have not been able to demonstrate monoclonality either in the lymphocytes or in the H, SR and L & H cells. Bearing in mind that HDNP involves the B-cell system, we screened a series of 82 cases for abnormalities in serum Ig levels (Hansmann et al. 1984). Most of the patients showed normal Ig levels, while only a few, mostly in stage IV, exhibited slightly reduced or elevated Ig levels. However, we recently found two patients with HDNP who showed selective reduction in Ig levels and lymphoid infiltrates in the lung. The present study deals with the morphological, immunohistochemical, and clinical findings in these two patients.

Material and methods

In a series of 540 cases of HDNP on file in the Lymph Node Registry in Kiel, two patients were found showing hypogammaglobulinaemia and lymphoid infiltrates of the lung. In the first case, seven lymph node biopsies and one lung biopsy were taken between 1972 and 1979. In the second case, one lymph node biopsy was taken in 1977 and one lung biopsy in 1986.

Clinical data

In case 1 a six-year old boy developed generalized lymph node enlargement without further clinical symptoms in 1972. No splenomegaly was found. Biopsy of a cervical lymph node revealed florid follicular hyperplasia and a few Hodgkin cell-like blasts in the interfollicular area. Although a firm diagnosis of HD could not be made, the boy was treated with 300 mg Endoxan. One month later laparotomy was performed and the spleen resected. Histologically, the mesenteric and paraaortic lymph nodes, liver, and spleen showed no infiltration by HD. Lymph node swelling recurred three times in the following four years, appearing bilaterally in the cervical, axillary, inguinal, and other regions. The biopsies were diagnosed as follicular

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Table 1. Specificities, dilutions, and sources of the monoclonal antibodies (mAb) used in paraffin sections

mAb	Dilution	Specificity	Source
Ki-B3	1:5000	pan-B cell	Institute of Pathology University of Kiel, FRG
4KB5 (CD45R)	1:100	B cells	Dakopatts, Denmark
L26	1:100	pan-B cell	Dakopatts, Denmark
MT1 (CD43)	1:100	pan-T cell	Laboserv Diagnostica, Giessen, FRG
UCHL1 (CDw45R)	1:100	pan-T cell	Dakopatts, Denmark
BerH2 (ED30)	1:4	Kil antigen	Prof. Dr. Stein, Inst. of Pathology, Free University of Berlin, FRG
LeuM1 (CD15)	1:100	SR cells, granulocytes	Becton, Dickinson, USA

hyperplasia or as chronic lymphadenitis. Up to 1976 the patient exhibited no fever, nightsweats, or weight loss. Tuberculin test (1/100) was positive at first biopsy, but negative two months later.

X-ray of the lung taken in 1976 revealed striped shadows similar to those seen in fungal or pneumocystic pneumonia. A lung biopsy was taken.

In 1979, seven years after the first biopsy, the patient experienced fever (>38° C) and "colic"-like pain in the region of the right hip joint. Pneumonia-like shadows were still present in X-rays of the lung. Leukocytes in the peripheral blood were 39.800/μl^3, with 33% lymphocytes. The serum gammaglobulin and IgG was diminished (Table 2). A submandibular lymph node biopsy showed the picture of HDNP. The clinical stage was IVB. Combined radiotherapy (total dose 32 Gy) and chemotherapy (modified MOPP scheme) led to complete remission. At thirty-four months after diagnosis of HD no relapse had occurred.

The second case was a 29-year-old man who had experienced frequent infections since birth, with recurrent coryza, enteritis, otitis, sinusitis, folliculitis, arthralgia of the hand joints, fever and neurodermatitis (Table 2). Prior to the diagnosis of HDNP, his serum immunoglobulins were markedly reduced (Table 2). Tuberculin test was not performed. A humoral immunodeficiency syndrome was diagnosed. Intermittent gammaglobulin substitution was performed.

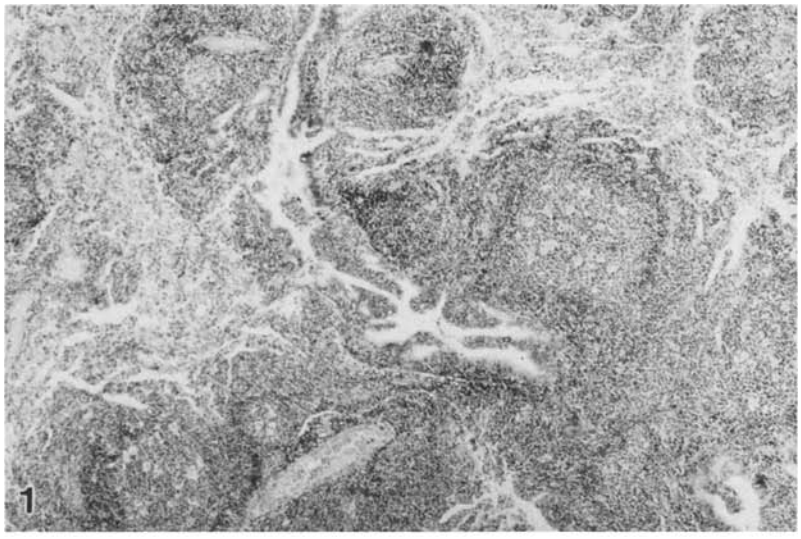
Swelling of the left axillary and bilateral swelling of the inguinal lymph nodes occurred in 1977. An axillary lymph node was excised and a diagnosis of HDNP was made. Lymphangiography revealed enlargement of the parapancreatic, the iliacal, and the para-aortic lymph nodes. Radiation therapy was performed and complete remission achieved.

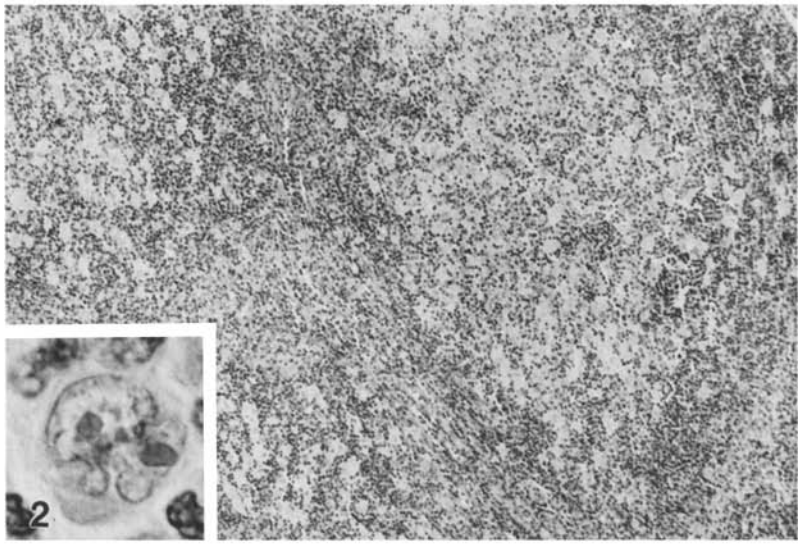
Seven years later (1984), the patient developed herpes zoster genitalis. In 1986 he developed dyspnoea. Intrapulmonary foci involving the left lung more than the right were demonstrated on X-ray. Open lung biopsy was performed. At that time the humoral immunodeficiency syndrome was still severe (Table 2). Tuberculin test was negative. A slight lymphopaenia was observed in the blood.

The tissues removed were fixed in formalin, embedded in paraplast, and sections were stained with H & E, Giemsa, PAS. A silver impregnation (Gomori) was performed. Immunohistochemical staining of paraffin sections was done using the peroxidase anti-peroxidase method (Mepham et al. 1979) and the ABC method (Guesdon et al. 1979). The following primary antisera were applied: anti-IgG, IgM, IgA, kappa, and lambda (Dakopatts, Copenhagen/Denmark; 1:100 in Tris-HCl buffer). Using monoclonal antibodies (mAb) the sections were treated

Table 2. Clinical manifestations

Sex/Age (Year)	Clinical signs	Chest radiography	Serum protein
Case 1:			
m/6 (1972)	asymptomatic; recurrent lymph node swelling	normal	Total protein 6.96 g% gammaglobulin 7.1%
/10 (1976)	Herpes zoster	lung infiltrates (x-ray)	Total protein 6.3 g% gammaglobulin 7.1%
/13 (1979)	Pel-Ebstein fever, colitis in right hip, itching, enlargement of submandibular lymph node	Persistence of shadows	Total protein 6.7 g% gammaglobulin 3.1% IgA 76 mg%; IgM 80 mg%, IgG 530 mg%
Case 2:			
m/29 (1977)	Frequent infections since birth, arthralgia in hand joints, swelling of axillary, iliacal and paraaortal lymph nodes	normal	Total protein 6.0–6.5 g% gammaglobulin 3.9–7.7% IgG 66–435 mg%
/36 (1984)	Herpes zoster genitalis	normal	not done
/38 (1986)	Sputum & dyspnea on exertion	lung infiltrates (x-ray)	Total protein 5.6 g% gammaglobulin 1.2% IgA 9 mg%, IgM 18 mg% IgG 260 mg%





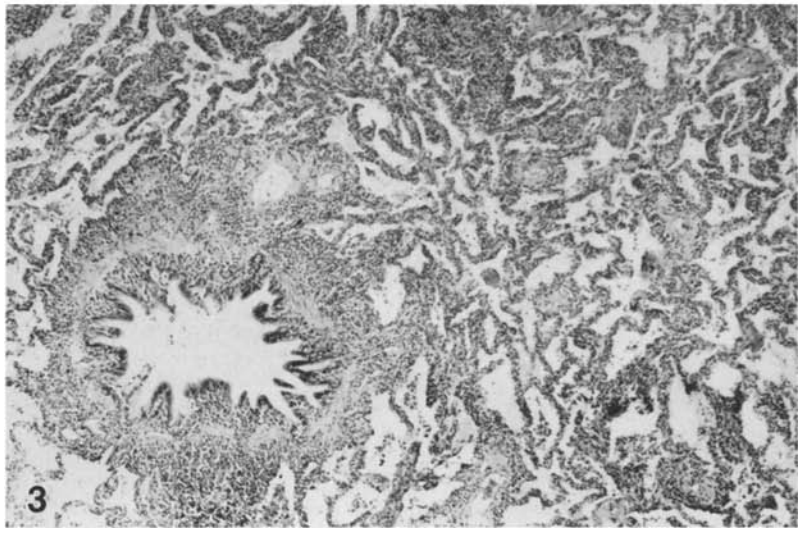
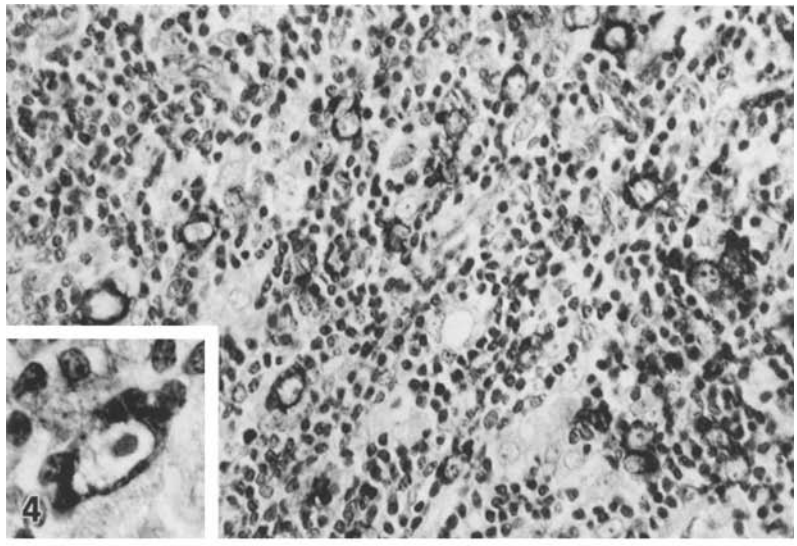


Fig. 1. Case 1: Florid lymphoid follicular hyperplasia of the lung. Giemsa × 56

Fig. 2. Case 2: Lymphocyte predominant Hodgkin's disease, nodular subtype in lymph node. Nodular infiltrates containing many epithelioid cells. *Inset*: L & H cell. H & E × 90. *Inset*: × 1400

Fig. 3. Case 2: Lymphoid interstitial pneumonia with diffuse infiltration by small lymphocytes. H & E × 56



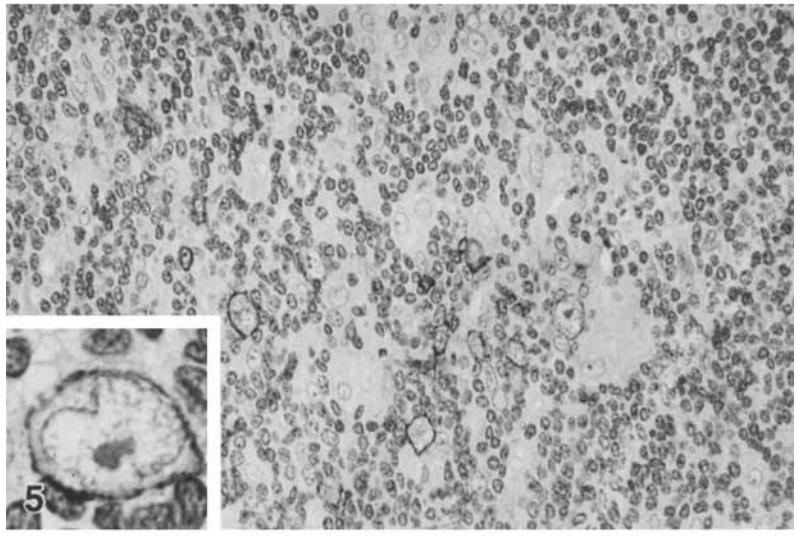


Fig. 4. Case 2: Lymphocyte predominant Hodgkin's disease, nodular subtype. L & H and Hodgkin cells showing a positive reaction with the anti-B-cell mAb Ki-B3. *Inset*: Hodgkin cell, positive with Ki-B3. Immunoperoxidase × 350. *Inset*: Immunoperoxidase × 1400

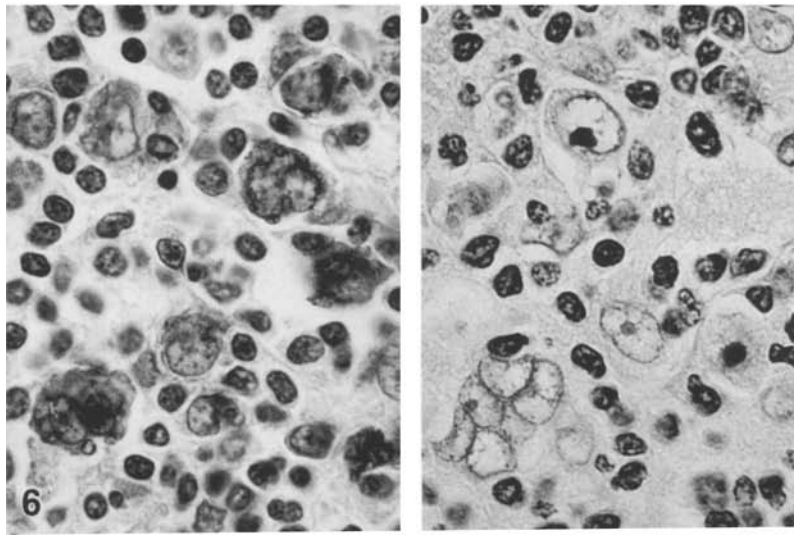


Fig. 5. Case 2: Lymphocyte predominant Hodgkin's disease, nodular subtype. Positive immunoreaction of the mAb L26 with L & H cells. *Inset*: L & H cell. Immunoperoxidase × 350. *Inset*: Immunoperoxidase × 1400

Fig. 6. Case 2: Immunoglobulin demonstration in lymphocyte predominant Hodgkin's disease, nodular subtype. L & H cells show intracytoplasmic positivity for the light chain kappa (*left*) but are negative for the light chain lambda (*right*). Immunohistochemical reaction (ABC method) × 880

according to the method of Stein et al. (1980). A list of mAb, their specificities, dilutions, and sources are given in Table 1.

Results

Histologically the first lymph node biopsy from case 1 (1972) showed a florid follicular hyperplasia with many tingible-body macrophages. The mantle-zones were often small and sometimes could not be identified. Some of the germinal centers showed a transition to progressively transformed germinal centers (PTGC). In the PTGC, lymphocytes dominated. No typical L & H or SR cells could be found in this biopsy. The seven subsequent lymph node biopsies showed the histological picture of a chronic nonspecific lymphadenitis with or without follicular hyperplasia consistently. Splenectomy and liver biopsy revealed no infiltation by HD.

The lung biopsy in 1976 exhibited a follicular interstitial lymphocyte infiltrate. The scattered follicles were located in the peribronchial and perivascular areas of the interlobular septa or around dilated lymph vessels. The follicles contained florid germinal centers with starry-sky macrophages and a few plasma cells. In some areas the nodular infiltrates formed large confluent lesions. The alveoli and bronchioles were often compressed by the lymphoid tissue (Fig. 1). No evidence of HDNP was found in the lung.

In 1979 another lymph node biopsy was performed. The lymph node architecture was completely effaced. The typical picture of HDNP with nodules composed of lymphocytes intermingled with epithelioid cells, H, SR, and L & H cells was found.

In case 2 the lymph node biopsy taken in 1977 exhibited HDNP (Fig. 2). PTGC were also present in this biopsy. The lung biopsy taken in 1986 showed an interstitial infiltrate (Fig. 3) composed chiefly of small lymphocytes and some plasma cells. Some eosinophils and mast cells were also found. The lymphatic vessels were often dilated. Occasionally, small germinal centers could be seen.

Immunohistologically the lymph node from case 1 (1972) shosed a polyclonal Ig-pattern. Many of the small lymphocytes were positive with the anit-B-cell mAb 4KB5. Only small numbers of T cells (MT1) could be detected.

In the lung biopsy the B cells, especially the plasma cells, showed a polyclonal Ig-pattern. IgM in particular was expressed in many plasma cells. Florid germinal centers also showed polytypic Ig positivity as well as a moderately positive reaction with the mAb Ki-B3. About 10% to 15% of the small lymphoid cells in the germinal centers were also positive with UCHL1. Moderate numbers of T cells (UCHL1+, MT1+) could be demonstrated around the germinal centers.

The lymph node biopsy from case 2 contained many L & H cells, which, together with the H and SR cells in the lymph node biopsy, showed surface membrane positivity for the B-cell markers Ki-B3 (Fig. 4) and L26 (Fig. 5). They were negative with the mAb 4KB5 and for the mAb LeuM1 (CD15) and BerH2 (CD30). Immunoglobulin staining revealed intracytoplasmic Ig-positivity for light chain kappa in some L & H cells, H and SR cells (Fig. 6), whereas the light chain lambda (Fig. 6) and IgM, IgG, IgA could not be demonstrated. No Ig-positive plasma cells were found. Some small lymphocytes were positive with the B-cell markers 4KB5, L26, and Ki-B3. A few UCHL1 and MT1 positive lymphocytes were seen, mainly located between the nodules.

In the lung biopsy polyclonal plasma cells were demonstrated, most of which expressed IgG. The few follicles contained kappa and lambda chain and IgM-positive cells but no IgA or IgG-positive cells. The follicles also reacted with the mAb Ki-B3. Most lymphoid cells in the interstitial areas showed marked UCHL1 positivity, while a lesser number were MT1 positive. The infiltrate was mainly composed of T cells. L & H, H and SR cells could not be detected by immunohistochemical staining.

Discussion

Two patients with HDNP in combination with hypogammaglobulinaemia and lymphoid infiltrates of the lung were investigated. In recent years more and more arguments have been put forward that HDNP is an entity distinct from other types of Hodgkin's disease, as originally proposed by Jackson and Parker (1947). This distinction is also reflected in the Lukes classification of Hodgkin's disease (1966). An argument for the B-cell derivation of L & H, H and SR cells is their ability to produce J chains (Poppema 1980; Hansmann et al. 1985; Stein et al. 1986). However, their clonality has not been demonstrated clearly. Poppema et al. 1979; Poppema 1980 described one type of light chain (mostly kappa chain) in individual L & H cells. In contrast, Stein et al. (1982) demonstrated both types of light chain in L & H, H, and SR cells using double staining methods. In this study we present one case (Case 2) in which the L & H type of SR cells were positive only for the light chain kappa. This immunophenotype was confirmed in

repeated staining procedures using two different techniques (PAP, Biotin-Avidin). The L & H, H, and SR cells in this case appear to produce this light chain, which is a common phenomenon in B-cell neoplasia. Unfortunately, the lymph node showing HDNP from patient 1 could not be studied immunohistochemically because no paraffin blocks were available. This monotypic Ig pattern in L & H, H, and SR cells in HDNP is unique in cases we have observed to date.

The lung infiltrates in both our cases did not show the picture of paragranuloma. They lacked L & H, H, and SR cells and did not exhibit monotypic Ig expression. The infiltrate in case 1 had large florid germinal centers such as are found in lymphoid hyperplasia of the lung and in low grade B cell lymphomas of the BALT (Addis et al. 1988; Li et al., in preparation). The latter was excluded because of its polytypic Ig expression. In case 2 only small follicles could be seen and the infiltrate was mainly localized in the interstitium as in an interstitial lymphocytic pneumonitis. Lymphoid hyperplasia of the lung has been described in the context of an immunodeficiency (Kohler et al. 1982; Yousen et al. 1985). Interstitial lymphoid pneumonitis is also known to occur in patients with immune defects caused, for example, by HIV infection (Joshi et al. 1987; Solal-Celigny et al. 1985; Yousen et al. 1985). The defect in the immune system in both our patients was indicated by the low serum immunoglobulin level (in patient 1 IgG, in patient 2 IgG, IgM, IgA). Defects in the humoral (Müller-Hermelink et al. 1986; Kaplan 1980; DeVita and Hellman 1982) and cellular (DeVita and Hellman 1982; Müller-Hermelink et al. 1986; Kaplan 1980) response have been reported in patients with types of Hodgkin's disease other than HDNP. The negative tuberculin reaction in both cases may be caused by an involvement of the cellular immunity as well. The frequent infections in both patients also fit in with their immunodeficient status. However, this appears to be an uncommon finding in cases of HDNP although the B-cell system seems to be primarily involved. In most cases, HDNP is a localized disorder diagnosed mainly in stage I (Hansmann et al. 1984). All other non-involved lymph nodes may compensate for this disorder and prevent an immune deficiency that is detectable in routine laboratory investigations such as electrophoresis and immunoelectrophoresis.

The two cases described here appear to represent a unique variant of HDNP. The triad of HDNP, lymphoid lung infiltrates and hypogammaglobulinaemia exhibited by these cases may reflect a generalized defect in the B-cell reaction.

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