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Function of the follicular dendritic cell in the germinal center of lymphoid follicles

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Summary. The authors made an immunocytochemical examination of the germinal centers (GCs) of (1) lymph follicles in physiological lymph nodes and (2) extra-nodal tissues of divergent diseases including thyroid disorders, rheumatoid arthritis, Warthin's tumor and Kimura's disease (Eosinophilic lymphfolliculoid granuloma). In these germinal centers, the presence of immunoglobulins (IgG and IgM), early acting complement components (C1q, C4, C3c,C3d), receptors for C3b and C3d and dendritic reticulum cell-l was demonstrated in lace-like network patterns which were proven electron-microscopically to coincide with the surface of follicular dendritic cells. IgE was distributed in a lace-like pattern in the GCs of proliferating follicles of Kimura's disease, in which the lysis of follicles was frequently observed. This lysis appeared to be related to the presence of complement components. In the germinal centers of extra-nodal tissues, including the thyroid tissues accompanying the lymph follicles, rheumatoid arthritis synovial tissues as well as Warthin's tumors, thyroglobulin, rheumatoid factor and salivary amylase were detected as specific antigens, occurring in lace-like patterns.

It is possible that follicular dendritic cells may play a role in the genesis of GCs and be responsible for the immune response through C3 receptors.

Key words: Germinal center - Immune complex - Complement components - Follicular dendritic cell

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Introduction

In lymph nodes and extra-nodal lymphoid tissues, secondary follicles with germinal centers (GCs) appear usually in response to antigenic stimulation. The significance of the GCs has been deeply studied from the standpoint of immunobiology. However, one of the problems which remains unsolved is the role of the stellate element, i.e, follicular dendritic cells (FDCs), welldeveloped in the light zone of GCs. The surface of these cells have been reported to contain receptors for some complement components (Gerdes and Stein, 1982).

The authors of this report made an immunocytochemical study of the lymph nodes and extra-nodal lymphoid tissues of four different diseases to advance our understanding about the role of FDCs in immune response.

Materials and methods

Specimens

Lymph nodes: Twenty specimens of tumor-free perigastric nodes removed from patients with gastric cancer were studied as samples of physiological (normal) nodes. Extra-nodal lymphoid tissues: 1) Thyroid tissues accompanying lymph follicles (LFs); 76 surgical specimens of thyroid tissues with secondary LFs were selected from 369 samples. Eleven samples were not fixed. 2) Synovial tissues of rheumatoid arthritis (RA); 20 RA synovial tissues, fulfilling diagnostic criteria for RA by the American Rheumatism Association (ARA, 1958) and containing LFs were selected from 148 synovectomized specimens. 3) Warthin's tumor; 24 surgical materials were utilized, of which four were not fixed. 4)Kimura's disease (Eosinophilic lymphfolliculoid granuloma); tissues from four cases, including one case recurrent on the opposite side (fresh material), were collected.

Methods

Immunocytochemical procedure: Materials for light microscopy were fixed in 10% formalin, routinely processed and embedded in paraffin. Sections were stained with hematoxylin-eosin and periodic acid-Schiff (PAS); moreover, the peroxidase anti-peroxidase (PAP) method was used for the detection of immunoglobulins (IgM, IgG, IgA, IgD and IgE), ferritin and lysozyme in the LFs. Freshly obtained materials were sliced and fixed for 6 hours in periodate-lysine-paraformaldehyde (PLP) containing 4% paraformaldehyde. After fixation, specimens were rinsed with 0.01M phosphate buffered saline, pH7.4, containing graded sucrose and frozen in an OCT compound (Miles Scientific, Naperville, IL) at -80°. The unfixed materials were frozen in the same manner. The indirect or direct immunoperoxidase stainings for light and electron microscopy were carried out as described previously (Farr and Nakane, 1981). Immunocytochemical reagents were tabulated in Table 1. Moreover, fresh specimens were also fixed with glutaraldehyde, refixed with osmium tetraoxide and finally embedded in Araldite-Quetol resin for electron microscopic examination. Furthermore, rabbit anti-human IgG, IgM, thyroglobulin (Tg), C3d antisera and goat anti-human C1q, C5 antisera were converted to $F(ab')_2$ fragments by pepsin treatment and conjugated with horseradish peroxidase, as described previously (Farr and Nakane, 1981; Yamakawa, 1985; Kasajima et al., 1986). Finally, PLP-fixed sections were used for the histochemical staining of acid phosphatase (Shibta, 1978) and beta-glucuronidase (Lorbacher, 1967). Control studies for the immunocytochemical staining were carried out as follows: 1) instead of first step antisera, normal rabbit, goat or mouse sera were used; 2) non-specific staining was checked by omitting the first step sera; 3) first step sera were absorbed by corresponding purified antigens. Simultaneously, specific reactions to each pure antigen were checked by using the double immunodiffusion method (Ouchterlony); 4) second step anti-sera were omitted; 5) endogenous peroxidase activity was checked by using only 3.3' -diamino- benzidine tetrahydrochloride (Dojin Co., Japan) reaction.

Results

I. Lymph nodes

1) Immunoglobulins: Immunostaining of IgM revealed its intercellular lace-like network in the GCs and also showed in the cytoplasms of some GC cells (Fig. 1a), while that of IgG was less prominent intercellularly, but rather frequent in the intracytoplasm. On the other hand, IgA was hardly seen in the GCs. Moreover, IgE and IgD were completely absent from the GCs in physiological lymph nodes. Immunoelectron microscopically, IgM and IgG were present as fine granules in the intercellular spaces and in the cytoplasms, especially on the cell surface of the FDC labyrinth structures. There were some lymphoid GC cells with positive granules in the perinuclear spaces and on the rough-surfaced endoplasmic reticulum, but none in the cytoplasm of FDCs (Figs. 1b, 2).

2) Complement components and complement receptors: For the detection of complement components, quickly frozen, non-fixed or PLP-fixed tissues were used. Complement components, C1q, C4, C3c and C3d (Fig. 3a), were clearly distributed in a lace-like network pattern within almost every GC. They appeared less frequently in the mantle zone and perivascular connective tissue surrounding the GCs. Through immunoelectron microscopic examination they were detected on the cell surface along the cytoplasmic projections of FDCs, and in the intercellular spaces between lymphoid cells (Fig. 3b). Moreover, in the mantle zone and primary follicles there were few positive foci of CR 1 and CR 2. C5 often showed patterns similar to early acting components (Fig. 4). Late acting components (C6, C8 and C9) were stained only in some of the tingible body macrophages (Fig. 5). C3b receptors (CR 1) and C3d receptors (CR 2) were distinctly recognized in the same fashion as complement components and were especially dense on the surface of FDCs (Figs. 6, 7). However, no iC3b receptors (CR 3) were found.

3) Dendritic reticulum cell-1 (DRC-1). Staining reaction to DRC-1 antibody appeared as a lace-like network pattern, the same as that of CR 1 or CR 2, within the GCs, but never outside the LFs except for a few positive foci in the matle zone and primary follicles (Fig. 8a). Immunoelectron microscopic examination revealed DRC-1 antigen located on the surface of FDCs with complicated cytoplasmic processes (Fig. 8b). But no positive reaction was evident in the cytoplasm of FDCs and lymphoid GC cells.

4) Immunostains of monoclonal antibodies to lymphocytes: Leu 1/OKT 3, Leu 2a/OKT 8, Leu 3a/OKT 4 and Leu 7 reacted with a variable numbers of cells in the GCs. In the physiologically normal lymph nodes, about twice as many Leu 3a/OKT 4-positive cells as Leu 2a/OKT 8-positive cells were detected. Leu 7 positive cells were scattered in the GCs. Some T cells and Leu 7-positive cells were evident along the surface of the FDC cytoplasmic processes.

5) Tingible body macrophages (TBM): The TBM varied in number and were irregularly scattered in the GCs. Immunocytochemically, the TBM frequently reacted to anti-ferritin, anti-lysozyme and Leu M2 antibodies, and were stained positively by acid phosphatase, beta-glucuronidase and PAS reaction. These positive reactions were not definitely confined to the GCs only.

The above-mentioned results are summarized in Table 2.

II. Extra-nodal lymph follicles

1) Immunoglobulins: Distribution of immunoglobulins in the GCs of the thyroid tissues accompanying LFs, RA synovial tissues and Warthin's tumor was patterned similarly to that of immunoglobulins in the lymph nodes. Through immunoelectron microscopic examination, IgM and IgG were detected inter- and intracellularly (Fig. 9). On the other hand, in the LFs of Kimura's disease and some cases of Warthin's tumor, IgE was distributed only in a lace-like network pattern without intracytoplasmic localization (Figs. 10a, 10b).

2) Complement components and complement receptors (CR 1, CR 2 and CR 3): The distribution and occurrence of complements in the GCs of thyroid tissues and RA synovial tissues were very similar to those of the lymph nodes. On the other hand, the majority of the complement components, including late complement components, appeared in a lace-like network pattern in the GCs of Kimura's disease. Some of the GCs were inclined to degenerate or collapse. CR 1 and CR 2 were distributed in a lace-like network pattern in the GCs of the four categories of disease examined. In Kimura's disease, there were some GCs in which these receptors could not be detected. CR 3 was not detected in any GCs.

3) Immunostains of DRC-1 and monoclonal antibodies to lymphocytes: FDCs in all follicles showed DRC-1 positivity, similar to the lymph nodes. DRC-1 was also observed in a few lymphoid aggregates of RA synovial tissues. Immunostaining of DRC-1 was never observed in the cytoplasms of FDCs and lymphoid cells.

Leu 1/OKT 3, Leu 2a/OKT 8 and Leu 3a/OKT 4 reacted rarely with the cell membranes in the GCs of thyroid tissues, RA synovial tissues and Warthin's tumor, respectively. The ratio between Leu 2a/OKT 8 and Leu 3a/OKT 4 -positive T cells varied from 1.5 to 4.0 and helper/inducer T cells were dominant over suppressor/cytotoxic T cells in the GCs of these disease. The only exception was Kimura's disease, in which the Leu 3a/OKT 4-positive T cells were found to be sparse in the GCs, although in a larger number than the Leu 2a/OKT 8-positive T cells. The distribution of Leu 7-positive cells in the GCs of the four diseases was similar to that of nodal follicles.

4) The detection of specific materials: In the thyroid tissues accompanying the LFs of the examined cases, only Tg was detected as an antigen in the GCs (Fig. 11a). No marked immunostaining of other reagents (thyroxine, thyrotrophin and thyroxine binding globulin) was seen in the GCs of thyroid tissues. Tg was positive with a lace-like network pattern similar to that of complement components and complement receptors. Tg was always negative intracytoplasmically.

In the RA synovial tissues, the rheumatoid factor (RF) was tested as an antigenic agent to LFs. RF showed as an antigenic agent in several GCs of most of the RA synovial tissues (Fig. 11b). It was also positive in the scattered lymphoid aggregates with lace-like network patterns. On the other hand, RF could be detected neither in non-RA synovial tissues nor in the GCs of non-RA lymph nodes.

Anti-human salivary amylase antiserum showed as a lace-like network pattern in the GCs of several cases of Warthin's tumor and was also positive in epithelial tumor cells (Fig. 11c). In this study, we could not test for antigenic agents in the case of Kimura's disease.

The above-mentioned results are summarized in Table 2.

Fig. 1. a. PLP-fixed cryostat section of lymph node. IgM immunostaining showing dendritic network patterns in many gernimal centers (arrow). Dark zones in the germinal centers are negative (asterisks). Many positive cells are found in the mantle zone (double arrow), paracortical and interfollicular areas. (Direct immunoperoxidase method; methylgreen counterstain; x 50). **b.** Immunoelectron staining for IgM in the perinuclear cystern (arrow) and rough endoplasmic reticula of germinoblastic cells, on the cell surface and in the intercellular space (asterisks) within a germinal center of the lymph node. (Direct immunoperoxidase method; x 8,000).

Fig. 2. Immunoelectron staining for IgG in the rough endoplasmic reticula of germinoblastic cells, on the cell surface and in the intercellular space within a germinal center of the lymph node. (Direct immunoperioxidase method; x 12,000).

Fig. 3. a. PLP-fixed cryostat section of lymph node. C3d immunostaining showing a lace-like pattern within a germinal center. (Direct immunoperoxidase method; methylgreen counterstain; x 600). **b.** Immunoelectron staining for C3d on the cell surface and in the intercellular space within a germinal center of a lymph node. (Direct immunoperoxidase method; x 5,000).

Fig. 4. PLP-fixed cryostat section of a lymph node. C5 immunostaining showing dendritic pattern within a germinal center. (Direct immunoperoxidase method; x 300).

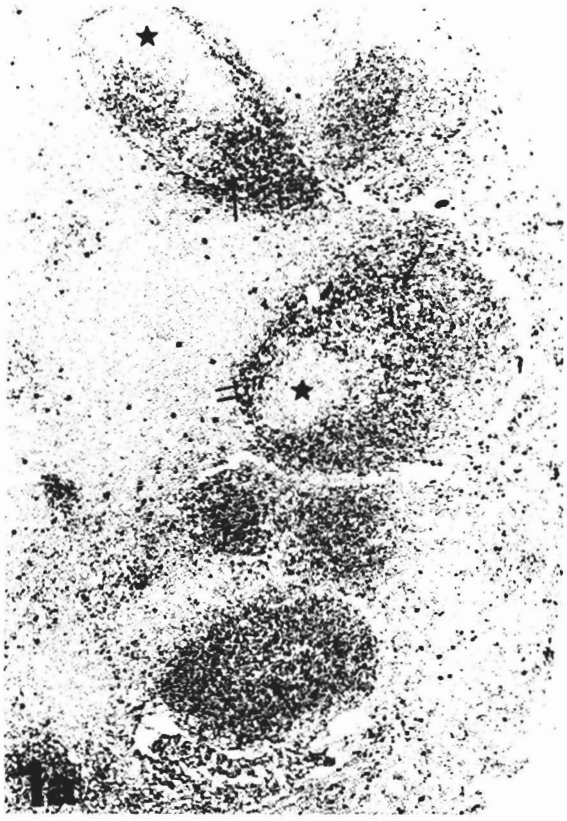
Fig. 5. PLP-fixed cryostat section of a lymph node. No marked immunostaining for C9 within a germinal center. A few positive macrophages are found within a germinal center (arrow) and in the interfollicular and paracortical areas. (Indirect immunoperoxidase method; methylgreen counterstain; x 150).

Fig. 6. PLP-fixed cryostat section of a lymph node. CR 1 immunostaining showing a lace-like pattern within a germinal center. (Indirect immunoperoxidase method; x 300).

Fig. 7. a. PLP-fixed cryostat section of a lymph node. CR 2 immunostaining showing a lace-like dendritic pattern within a germinal center. (Indirect immunoperoxidase method; x 300). **b.** Immunoelectron staining for CR 2 on the cell surface of lymphoid cells and in the labyrinth structure of a follicular dendritic cell (FDC) within a germinal center of a lymph node. (Indirect immunoperoxidase method; x 4,000).

Fig. 8. a. PLP-fixed cryostat section of a lymph node. DRC-1 immunostaining showing a lace-like network pattern within a germinal center and a part of the mantle zone. (Indirect immunoperoxidase method; methylgreen counterstain; x 300). **b.** Immunoelectron staining for DRC-1 on the cell surface, including the labyrinth structure of a follicular dendritic cell (FDC, arrow) within a germinal center. (Indirect immunoperoxidase method; x 5,000).

Fig. 9. IgM immunostainings showing a lace-like pattern within the germinal centers of chronic thyroiditis (9a; paraffin-embedded section; PAP method; methylgreen counterstain; x 300), Warthin's tumor (9b; paraffin-embedded section; PAP method; hematoxylin counterstain; x 700), rheumatoid arthritis (9c; PLP-fixed cryostat section; direct immunoperoxidase method; methylgreen counterstain; x 300) and Kimura's disease (9d; PLP-fixed cryostat section; direct immunoperoxidase method; methylgreen counterstain; x 150).



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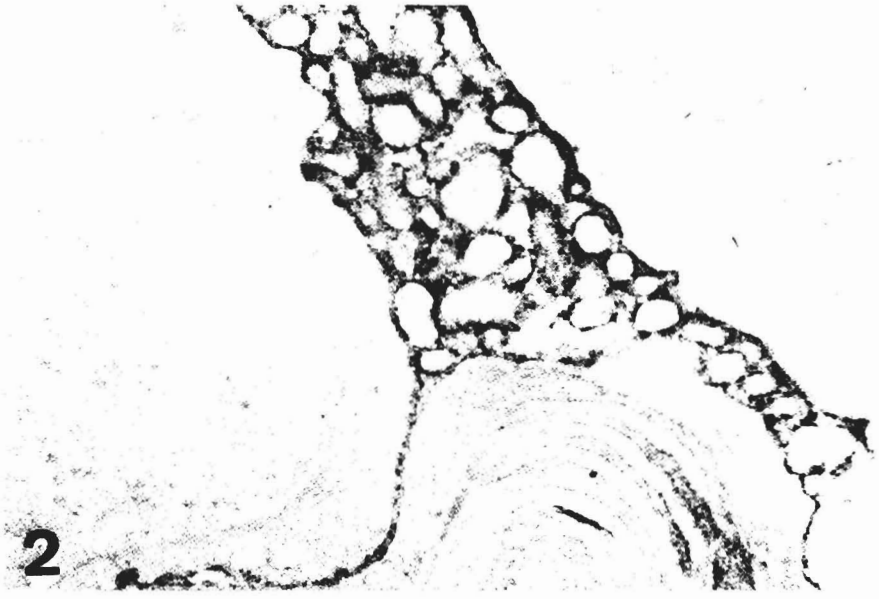
1b



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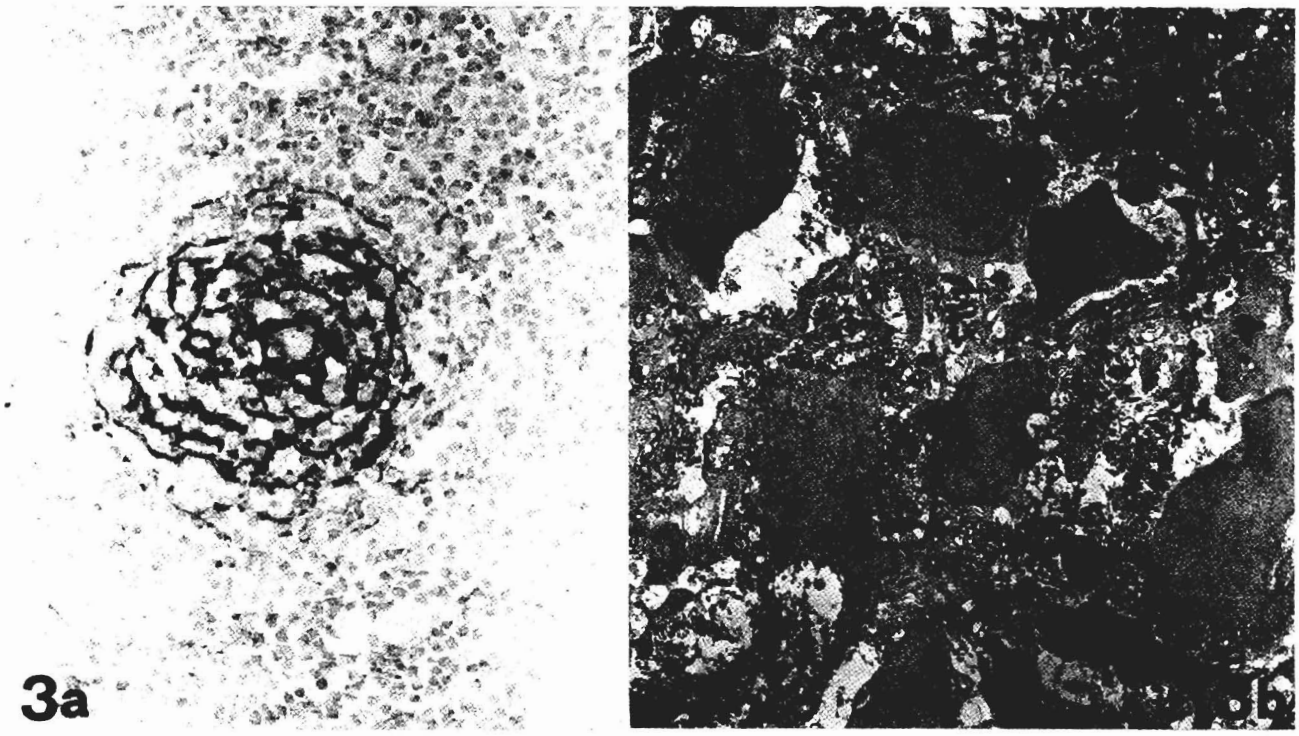
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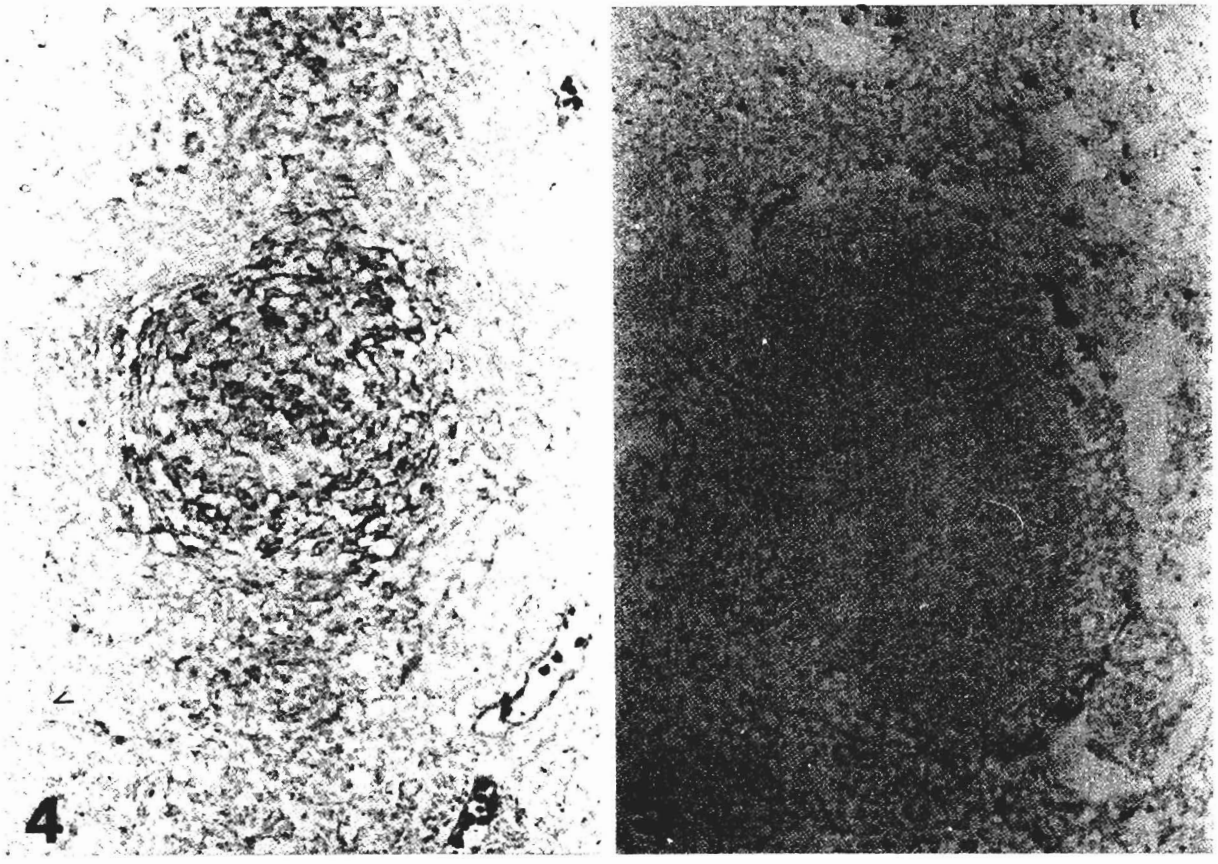
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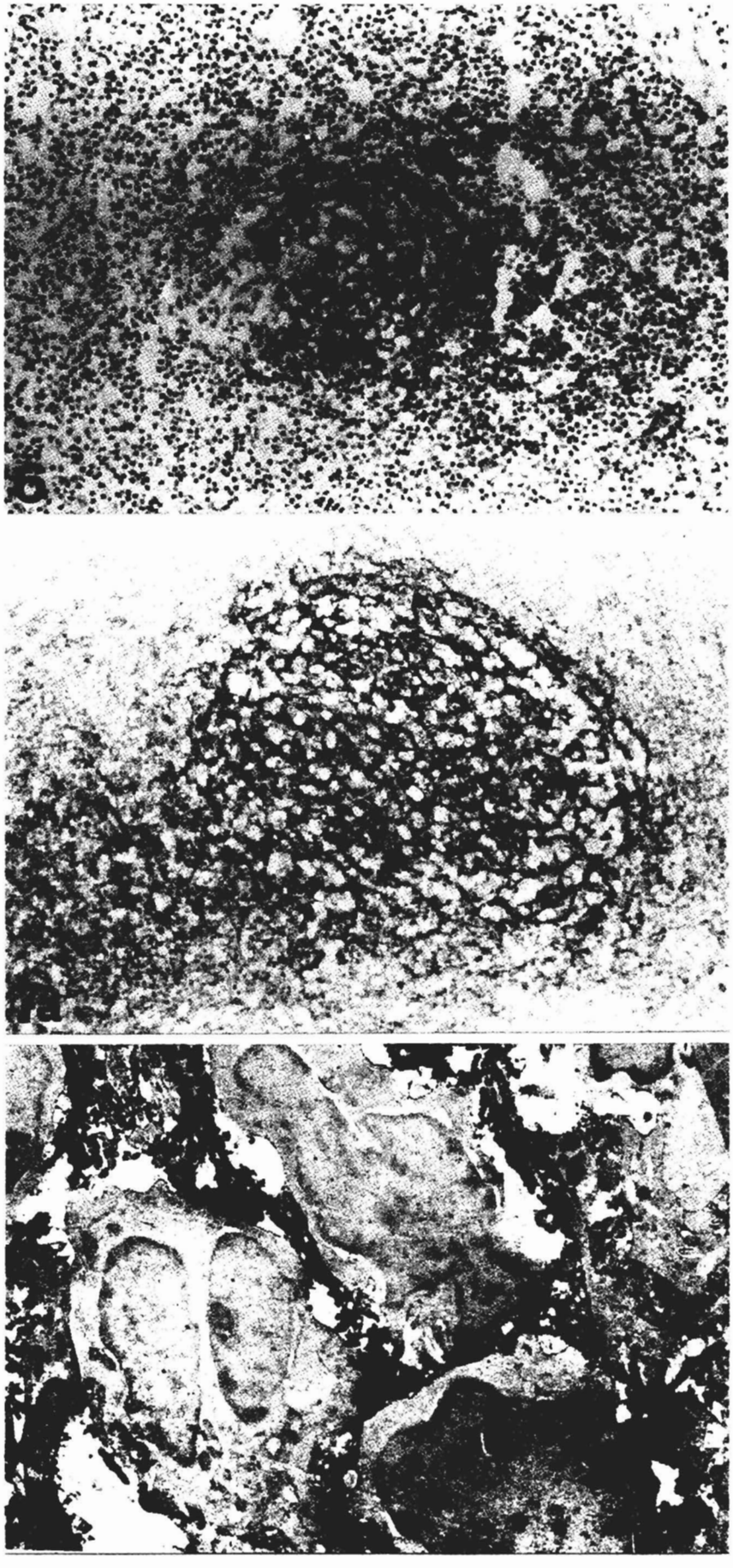
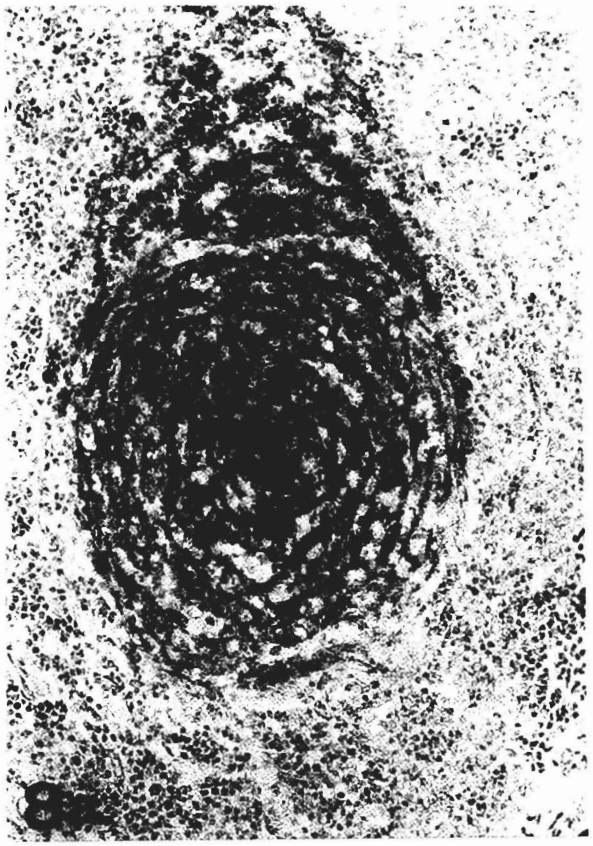
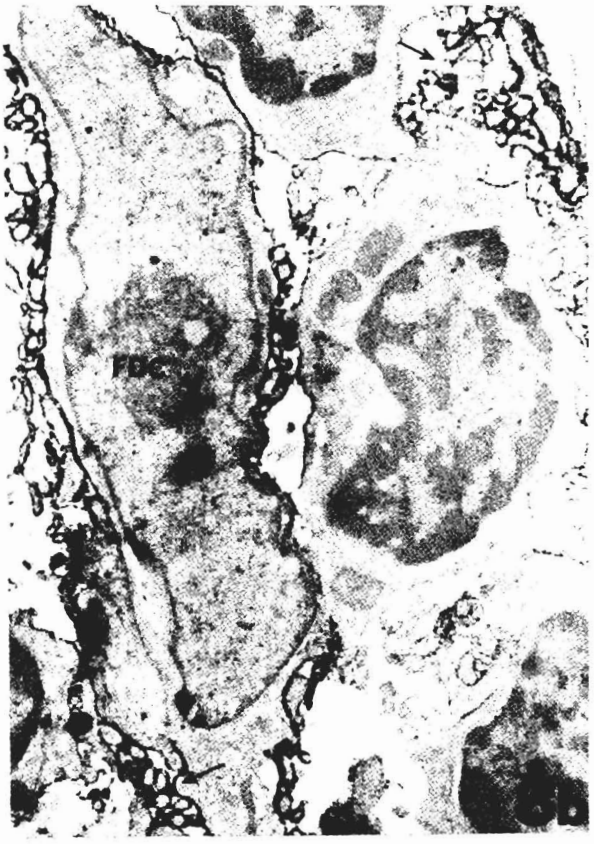
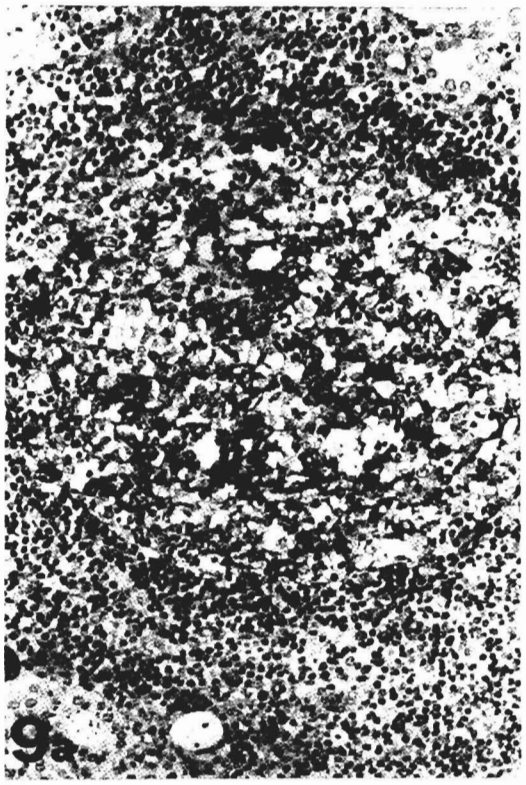





FDC



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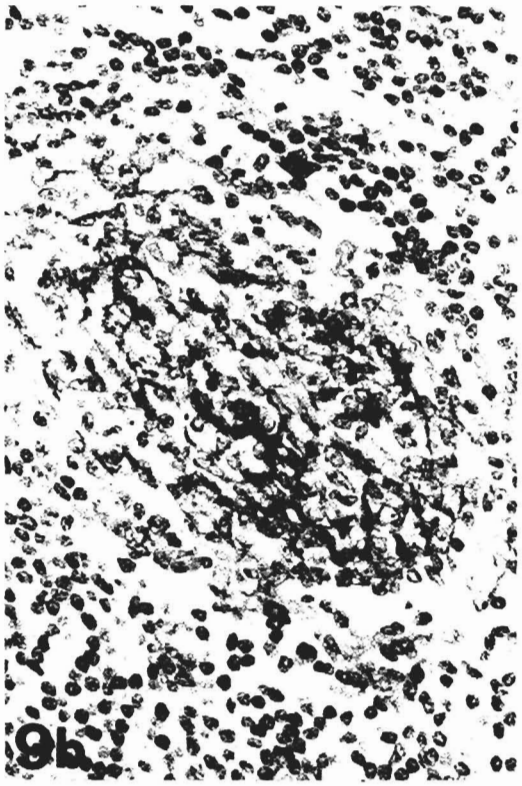

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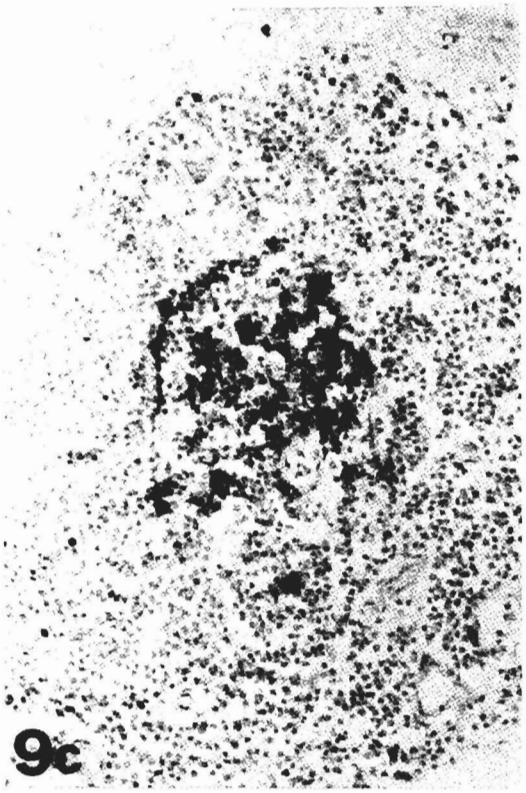

9c

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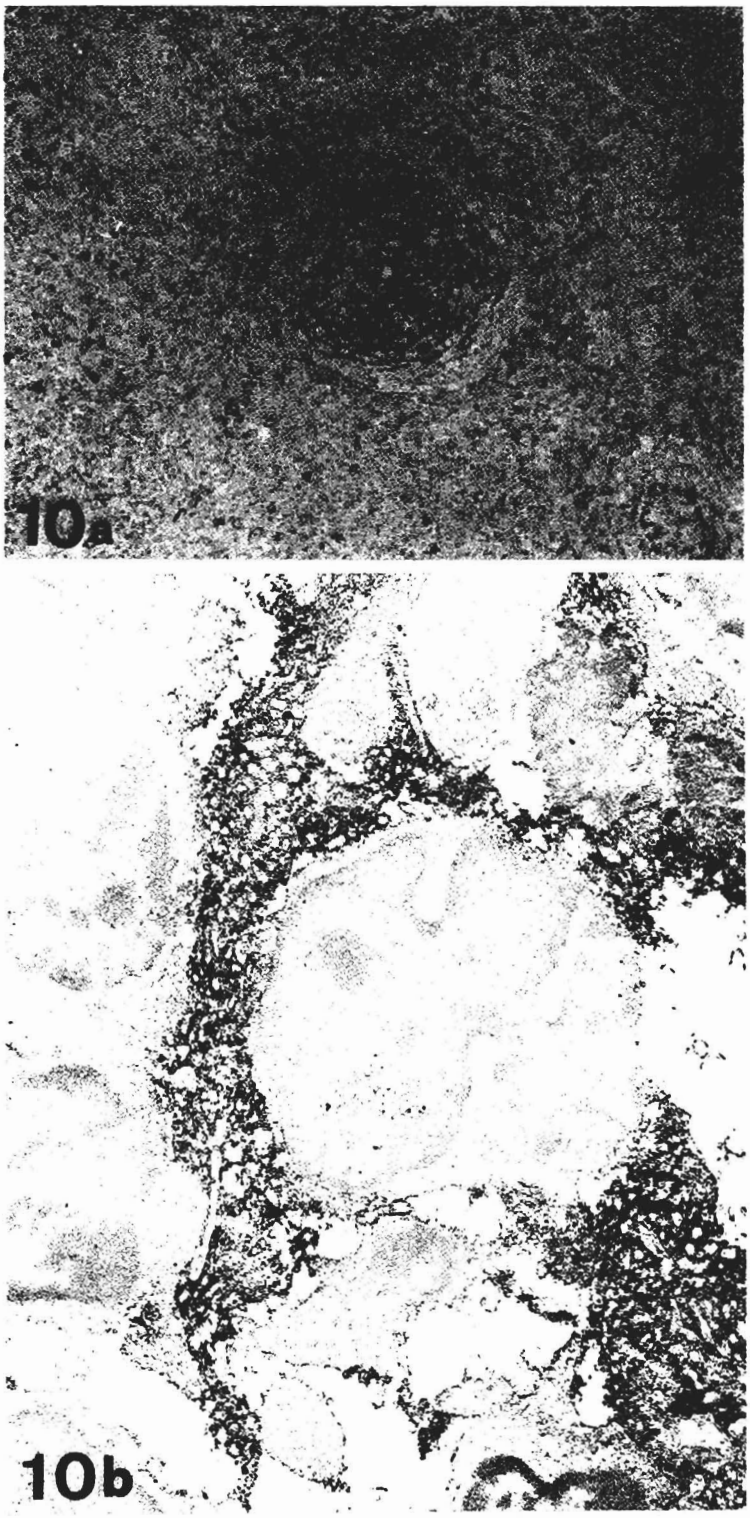
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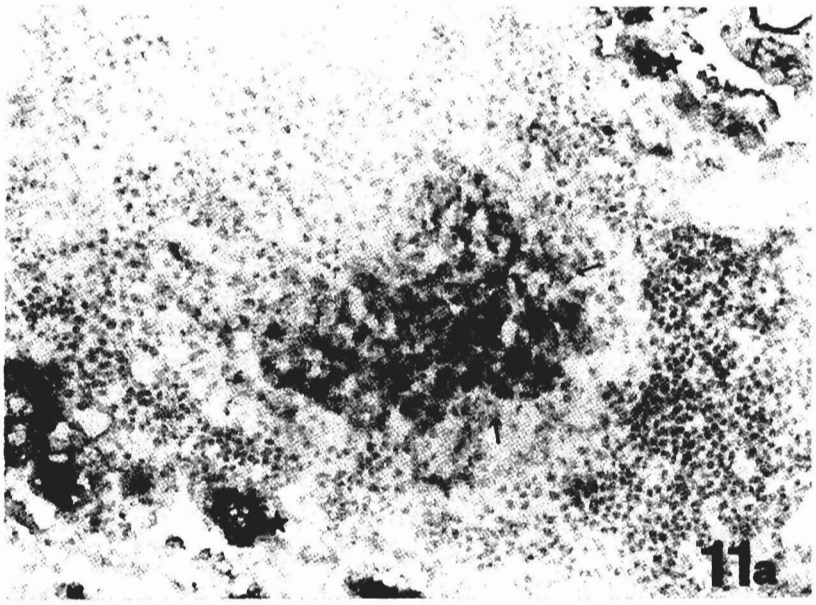

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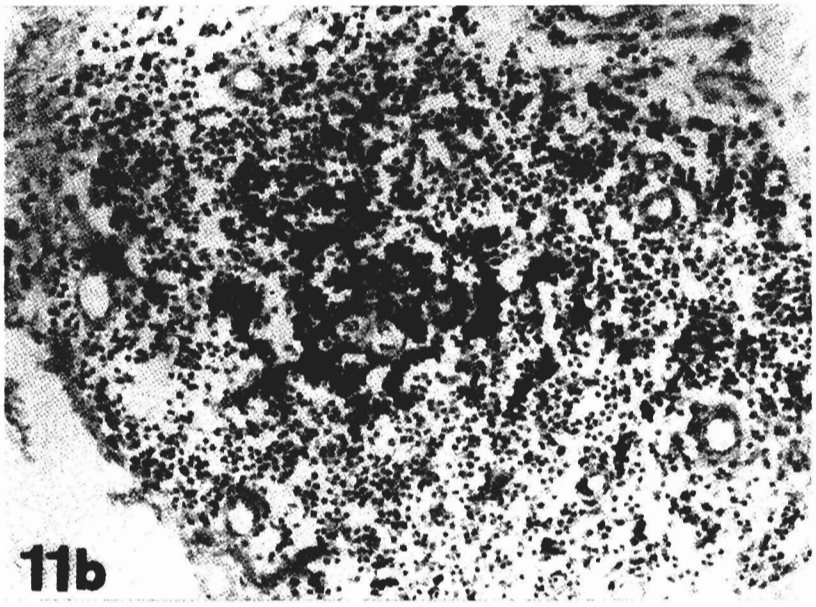
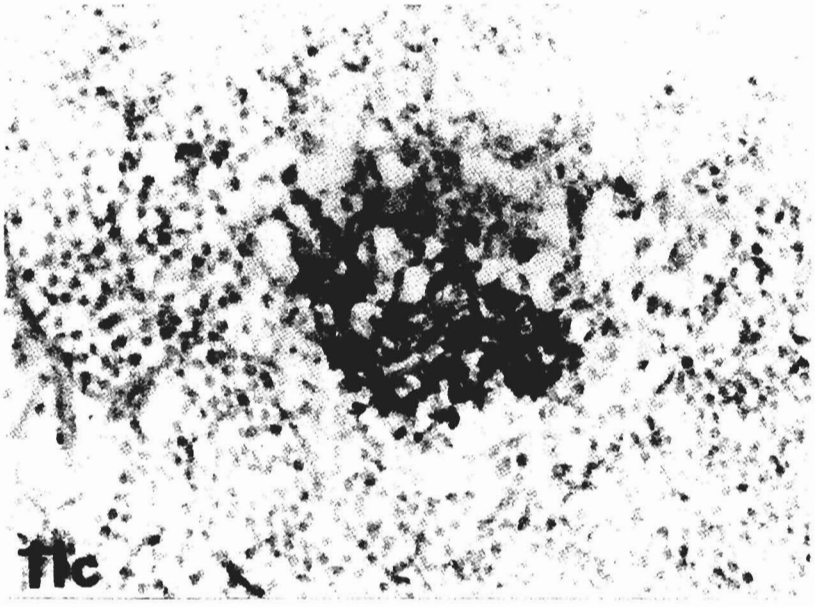


11b



11c

Fig. 10. a. PLP-fixed cryostat section of Kimura's disease. IgE immunostaining showing a lace-like dendritic pattern within a germinal center. (Indirect immunoperoxidase method; methylgreen counterstain; x 300). **b.** Immunoelectron staining for IgE on the cell surface and in the intercellular space within a germinal center. (Indirect immunoperoxidase method; x 400).

Fig. 11. PLP-fixed cryostat sections of chronic thyroiditis (11a), rheumatoid arthritis (11b) and Warthin's tumor (11c). Thyroglobulin (11a; direct immunoperoxidase method; x 300), rheumatoid factor (11b; indirect immunoperoxidase method; x 300) and salivary amylase (11c; indirect immunoperoxidase method; x 500) immunostainings showing a lace-like pattern within the germinal centers. Arrows and asterisks in Fig. 11a indicate the positive stainings for thyroglobulin of a germinal center and colloid follicular epithelia. Methylgreen counterstain.

Table 1. List of antisera used in this study

Antibodies		Sources
Antisera to immunoglobulins		
Rabbit antihuman	IgG, IgM, IgE,	DAKOPATTS
Rabbit antihuman	IgA, IgD	Boehringerwerke
Monoclonal antibodies		
Mouse antihuman	Leu1, Leu2a, Leu3a, Leu7	Becton-Dickinson Monoclonal Center
	LeuM1, LeuM2, LeuM3, LeuM4, LeuM5	Becton-Dickinson Monoclonal Center
	OKT3, OKT4, OKT8	Ortho Diagnostics Systems
	C3bR (CR1)	DAKOPATTS
	C3dR (CR2), C3biR (CR3)	Becton-Dickinson Monoclonal Center
	Rheumatoid factor (IgM)	Chemicon International/Cal-Med
	DRC-1	DAKOPATTS
Antisera to complement components		
Rabbit antihuman	C1q, C5, C3d	DAKOPATTS
	C3c, C3 activator	Boeringerwerke
Goat antihuman	C9, properdine	Miles Scientific
	C6, C8, β1H globulin	Cappel Lab.
	C4, C3b inactivator	Kent Lab.
Antisera to other agents		
Rabbit antihuman	Thyroglobulin, TSH, TBG, Thyroxine	DAKOPATSS
	Thyroxine	Immulok
	Salivary amylase	Nordic Immunoligical Lab.
	Lysozyme	DAKOPATSS
	Ferritin	DAKOPATSS
Other sera and reagents		
Swine anti-rabbit immunoglobulins		DAKOPATTS
HRP conjugated sheep anti-mouse immnoglobulins		Amersham International
HRP conjugated rabbit anti-goat IgG		Cappel Lab.
HRP conjugated swine anti-rabbit immunoglobulins		Cappel Lab.
Peroxidase-antiperoxidase complex		DAKOPATTS

Table 2. Reactivity to various antisera in the germinal center of (1) lymph node, (2) thyroid, (3) rheumatoid arthritis, (4) Warthin's tumor and (5) Kimura's disease

	(1)	(2)	(3)	(4)	(5)
IgG	+ +	+	+	+	+
IgM	+ + +	+ + +	+ + +	+ + +	+ + +
IgA	+	+	+	+	+
IgD	−	−	−	−	−
IgE	−	−	−	− ~ + + +	+ + +
DRC1	+ + +	+ + +	+ + +	+ + +	+ + +
CR1	+ + +	+ + +	+ + +	+ + +	+ + +
CR2	+ + +	+ + +	+ + +	+ + +	+ + +
CR3	−	−	−	−	−
C1q	+ +	+ +	+ +	+	+
C4	+	+	+	+	+
C3c	+	+	+	+	+
C3d	+ + +	+ + +	+ + +	+ + +	+ + +
C5	+	+	+	+	+
C6	−	−	−	−	− ~ +
C8	−	−	−	−	− ~ +
C9	−	−	−	−	− ~ +
Prop	−	−	−	−	− ~ +
C3act	−	−	−	−	−
C3bINA	+	+	+	+	+
β1H	−	−	−	−	− ~ +
Tg	−	+	−	−	−
RF	−	−	+	−	−
Amy	−	−	−	+ ~ −	−

Discussion

Recently, it has been experimentally proven that the localization sites and distribution of antigens coincide with those of antibodies, and that the antigens or immune complexes are closely related to the FDCs of GCs (Papamichail et al., 1975; Imai et al., 1983). Moreover, it has been reported by many researchers that FDCs play important roles, including antigen/immune complex trapping, antigen/immune complex presentation and promoting the immune response in lymph nodes (Klaus et al., 1980; Steinman et al., 1980; Hoefsmit et al., 1980; Tew et al., 1980; Gerdes et al., 1982). Moreover, it was Shown that FDCs have complement receptors for C3b and C3d which could bind to immune complexes. Similar reports have been published by many researchers (Gajl-Peczalska et al., 1969; Gerdes et al., 1982; Yamakawa, 1985; Kasajima et al., 1986). The authors of this study, using immunohistochemical techniques, could also detect C3b and C3d receptors on the surface of FDCs in the GCs of lymph nodes and extra-nodal lymphoid tissues.

In the GCs, there were many B lymphocytes mixed with T lymphocytes (both suppressor and helper T lymphocytes) (Poppema et al., 1981). Two types of T cells with a close relationship to FDCs in the GCs were recognized in this study by an immunocytochemical method using monoclonal antibodies. There are many reports concerning immunohistological studies on the localization of complement components, especially C3 and C4 in the liver and kidney (Nagura et al., 1985). On the other hand, our knowledge about complement components and their receptors in lymph nodes is still insufficient. It is very difficult to detect complement components in the usual fixed materials; therefore, we used fresh frozen or mild PLP-fixed frozen sections. Complement activation is caused by many kinds of agents, especially immune complexes containing IgM or IgG in the classical pathway and IgA or IgE in the alternative pathway (Miller et al., 1973).

In the GCs of physiological lymph nodes, only early activating components of the classical pathway, C1q, C4, C3c and C3d, were found in the intercellular space and on the cell surface in the GCs. C5 had the same pattern. From the remarkable presence of early components, especially C3d, on the labyrinth structures of FDCs, it can be surmised that FDCs possess C3d receptors on their cell surface and that immune complexes bind to FDCs through the C3b and C3d receptors.

Late components of complements, e.g. C6, C8 and C9, which have a cytolytic function, have never been detected within GCs, though they have been identified in scattered macrophages or leukocytes outside the LFs of lymph nodes. It could be suggested that there are too few complements to be detected in frozen tissue sections or that the cytolytic complement activation has been blocked by complement inhibitory components. In addition, complement components of the alternative pathway could not be detected in the GCs of physiological lymph nodes, thyroid tissues, RA synovial tissues and Warthin's tumor.

On the other hand, almost every component of the two pathways is found in many GCs of Kimura's disease (Kimura et al., 1948; Ishikawa et al., 1981). Kimura's disease is histologically characterized by the occurrence of

predominant LFs in GCs and by an infiltration of eosinophils and mast cells. Moreover, in the peripheral blood of patients with Kimura's disease, a high dose of IgE was detected and IgE appeared immunohistologically in plasma cells and in the GCs of tumor tissue. We also have observed that IgE was distributed in lace-like networks without intracytoplasmic localization, not only in the GCs but also in the infiltrating plasma cells. On the basis of the presence of all complement components, it seems possible that the LFs appear after the stimulation of some agents, for example parasitic or fungal infection, and delayed allergic reaction, while the LFs in Kimura's disease might degenerate or disappear by complement activation followed by IgE in the follicles. Other classes of immunoglobulins are not obvious, because Ishikawa et al. (1981) reported that immunohistochemical examination revealed only a small number of lymphocytes.

The above-mentioned results suggest that complement components are important factors in the correlation with antigen-antibody reaction or immune complex-trapping and retaining. Recently, many complement receptors on the cell surface have been reported, especially C3b (CR 1) and C3d (CR 2) which have been detected on the surface of FDCs in the GCs. Moreover, C3d has been found in remarkable amounts in the labyrinth structure of FDCs.

It can be concluded that FDCs play the most important role in immune response in the GC, which in turn plays a central role in the defence mechanism against organisms.

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