Ultrastructural, Cytochemical, and Membrane Surface Marker Characteristics of the Atypical Lymphocytes in Infectious Mononucleosis

By Robert W. McKenna, Janet Parkin, Kazimiera J. Gajl-Peczalska, John H. Kersey, and Richard D. Brunning

Atypical lymphocytes from nine young adults with acute infectious mononucleosis (IM) were studied for morphologic, ultrastructural, cytochemical, and membrane surface marker characteristics. There was an absolute increase in T lymphocytes in the patients. Atypical lymphocytes accounted for 83%-96% of the lymphocyte population. These lymphocytes contained cytoplasmic inclusions which ranged in size from 1000 to 6000 Å, were usually membrane bound, and consisted of parallel arrays of microtubule-like structures. The inclusions, which have been referred to as parallel tubular arrays (PTA), were found in 15%-75% of the lymphocytes from the IM patients. Ultrastructural cytochemical methods demonstrated acid phosphatase activity within many of the membrane-bound PTA. The function of the PTA is unknown. Since they were observed only in the lymphocytes which appeared to correspond to the atypical lymphocytes on light microscopy, the majority of which typed as T cells, there appears to be an association between PTA and T lymphocytes. It is possible that PTA identify a specific subset of T lymphocytes which is expanded in IM. Alternatively, PTA may be a transient finding in lymphocytes appearing only in certain biologic states of the cell such as during T-lymphocyte activation.

INFECTIOUS MONONUCLEOSIS (IM) is a self-limited lymphoproliferative disease caused by the Epstein-Barr virus (EBV) and characterized by intense lymphoproliferation in lymph nodes and other lymphoid tissues and the appearance of large numbers of atypical lymphocytes in the blood. It has recently been shown that the atypical lymphocytosis in IM is primarily due to an expansion of T lymphocytes; an increase in B lymphocytes has also been reported. Some investigators have proposed that the atypical lymphocytes of T-cell origin represent a cellular immune response against EBV-associated antigens or cells infected with EBV and that the atypical lymphocytes of B cell origin represent EBV-infected cells.

In previous reports from this laboratory, lymphocytes containing cytoplasmic inclusions of microtubule-like structures (parallel tubular arrays, PTA) have been described. These structures were noted in an increased number of lymphocytes in patients with IM and in patients with a chronic lymphoprolif-
The patient population of this study consisted of nine students who presented at a University Student Health Service with typical clinical and peripheral blood manifestations and positive serologic reactions for acute IM. Eight of the nine patients complained of excessive tiredness of 3-9 days duration. Eight complained of a sore throat and had physical evidence of pharyngitis. In one patient, pharyngitis was the only symptom. Eight patients had lymphadenopathy. All patients exhibited an absolute lymphocytosis with a high percentage of atypical lymphocytes. All had positive serologic tests for IM with the Monosticon DRI-DOT differential slide test from Organon. All patients were 19-23 yr of age. Eight were male; one was female.

Blood was drawn for studies from each patient within 24 hr of their first seeking medical attention. All studies were repeated on a second blood specimen obtained 24 hr after the first. In addition, a specimen was drawn for studies at 5 days from two of the patients and at 7 days from three of the patients. Identical studies were performed on four age-matched student controls who had no evidence of recent illness. Complete blood counts and differential leukocyte counts were performed on all of the patients and control subjects each time a specimen was collected. The morphology of the lymphocytes was studied in Wright-Giemsa stained smears. The lymphocytes were also evaluated for PAS positivity and for acid phosphatase, β-glucuronidase, and nonspecific esterase activity. The peripheral blood lymphocytes were collected and processed for ultrastructural study by methods previously described. In addition, ultrastructural cytochemistry for demonstration of acid phosphatase activity was performed on three of the patients in the following manner, using the method of Katayama and associates. Buffy coats were fixed in modified Karnovsky fixative (2% paraformaldehyde and 2% glutaraldehyde in 0.1 M sodium cacodylate-HCl buffer at pH 7.3) for 1 hr at 4°C, washed overnight at 4°C in 0.05 M sodium cacodylate-HCl buffer with 0.2 M sucrose added, and diced into 0.5 x 0.5 mm blocks. These blocks were incubated for 30 min at room temperature with constant agitation in a modified Gomori medium consisting of 30 mg lead nitrate in 25 ml 0.05 M sodium acetate buffer, pH 5.0, containing 7.5% sucrose and 2.5 ml of 3% β-glycerophosphate as substrate. Control blocks were incubated in the medium without the substrate and also in the medium without the lead nitrate. After incubation, the blocks were rinsed briefly in 0.05 M sodium acetate buffer, pH 5.0, and then immediately postfixed in 1% buffered OsO4 at 0°C for 1 hr. They were then processed for electron microscopy in the regular manner.

Lymphocyte suspensions were prepared for cell membrane marker studies from heparinized peripheral blood by use of a Ficoll Hypaque density gradient technique. Suspensions were preincubated with latex particles to distinguish contaminating monocytes from lymphocytes. The presence of surface immunoglobulin on the lymphocytes was determined by direct immunofluorescence microscopy using monospecific antisera to γ, μ, and α heavy chains and κ and λ light chains as previously reported. The assay of sheep erythrocyte rosette formation was performed as previously described, with the addition of a 5-min lymphocyte incubation at 37°C prior to incubation at 4°C. In one patient the suspension of rosetted lymphocytes was processed for ultrastructural studies. Complement receptors were assayed by preparing a fresh chicken erythrocyte-antibody (IgG) complement complex (cEAC') and performing a combined rosette assay as previously described. An assay using chicken erythrocyte-antibody (IgG), i.e., cEA, without complement was performed simultaneously to act as a control for the complement receptor assay in five of the patients and in three of the control subjects. Chicken erythrocytes were used in the combined assay because they do not bind spontaneously to human lymphocytes and because they are morphologically distinct from sheep erythrocytes. Lymphocyte Fe receptors were assayed using aggregated human IgG following the method of Dickler and Kunkel.
Table 1. Studies on Blood Lymphocytes in Infectious Mononucleosis Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total Leukocytes/cu mm</th>
<th>Lymphocytes/cu mm</th>
<th>Atypical Lymphocytes (%)</th>
<th>Lymphocytes With Granules (%)</th>
<th>Lymphocytes With PTA (%)</th>
<th>E Rosettes (T Cells)</th>
<th>Surface Immunoglobulin</th>
<th>Complement Receptors</th>
<th>Fc Receptors</th>
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<td>89</td>
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<td>4,400 (71)</td>
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<td>57</td>
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<td>(day 5)</td>
<td>8,600</td>
<td>4,600</td>
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<td>65</td>
<td>30</td>
<td>2,900 (64)</td>
<td>184 (4)</td>
<td>230 (5)</td>
<td>1,420 (31)</td>
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<td>3,600</td>
<td>85</td>
<td>58</td>
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<td>6</td>
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<td>93</td>
<td>74</td>
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<td>3,600 (66)</td>
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<tr>
<td>(day 5)</td>
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<td>62</td>
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<td>(day 7)</td>
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<td>3,500</td>
<td>83</td>
<td>71</td>
<td>40</td>
<td>2,600 (73)</td>
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<td>245 (7)</td>
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<td>95</td>
<td>75</td>
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<td>10,400 (79)</td>
<td>523 (4)</td>
<td>524 (4)</td>
<td>1,050 (8)</td>
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<tr>
<td>(day 7)</td>
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<td>6,200</td>
<td>90</td>
<td>60</td>
<td>Not tested</td>
<td>4,700 (77)</td>
<td>186 (3)</td>
<td>558 (9)</td>
<td>496 (8)</td>
</tr>
<tr>
<td>9</td>
<td>7,900</td>
<td>4,000</td>
<td>83</td>
<td>57</td>
<td>15</td>
<td>2,500 (63)</td>
<td>240 (6)</td>
<td>280 (7)</td>
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<tr>
<td>(day 7)</td>
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<td>4,300</td>
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<td>20</td>
<td>2,800 (64)</td>
<td>516 (12)</td>
<td>516 (12)</td>
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*Laboratory normals: E rosettes, 750–3000/cu mm; surface immunoglobulin, 110–730/cu mm; complement receptors, 105–600/cu mm; Fc receptors, 120–980/cu mm.

Table 2. Studies on Blood Lymphocytes in Control Subjects

<table>
<thead>
<tr>
<th>Controls</th>
<th>Total Leukocytes/cu mm</th>
<th>Lymphocytes/cu mm</th>
<th>Atypical Lymphocytes (%)</th>
<th>Lymphocytes With Granules (%)</th>
<th>Lymphocytes With PTA (%)</th>
<th>E Rosettes (T Cells)</th>
<th>Surface Immunoglobulin</th>
<th>Complement Receptors</th>
<th>Fc Receptors</th>
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</thead>
<tbody>
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<td>1</td>
<td>6,100</td>
<td>3,100</td>
<td>12</td>
<td>6</td>
<td>5</td>
<td>1,900 (61)</td>
<td>186 (6)</td>
<td>310 (10)</td>
<td>496 (16)</td>
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<tr>
<td>2</td>
<td>9,600</td>
<td>1,900</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>1,300 (69)</td>
<td>228 (12)</td>
<td>190 (10)</td>
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<td>18</td>
<td>14</td>
<td>10</td>
<td>1,200 (77)</td>
<td>160 (10)</td>
<td>144 (9)</td>
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<tr>
<td>4</td>
<td>6,600</td>
<td>3,200</td>
<td>29</td>
<td>28</td>
<td>10</td>
<td>1,900 (59)</td>
<td>352 (11)</td>
<td>288 (9)</td>
<td>480 (15)</td>
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</table>

*Laboratory normals: E rosettes, 750–3000/cu mm; surface immunoglobulin, 110–730/cu mm; complement receptors, 105–600/cu mm; Fc receptors, 120–980/cu mm.
RESULTS

Leukocyte Counts and Morphology

The blood counts of the nine patients are shown in Table 1. In all instances, the initial and 24-hr values for all tests performed on the patients showed minimal differences. An average of the two values is given for all parameters studied. The values for those patients tested at 5 or 7 days are listed separately. Initial total leukocyte counts were 7900-14,900/cu mm. All patients had an absolute lymphocytosis of 3600-13,100/cu mm. Atypical lymphocytes accounted for 83%-96% of the lymphocyte population. The predominant atypical lymphocyte in all of the patients was the type II reactive lymphocyte of Downey and McKinlay (Fig. 1). Occasional Downey type III reactive lymphocytes were present in some of the patients (Fig. 2). It was found that 57%-75% of the lymphocytes contained azurophilic granules in the cytoplasm. The granulation was present predominantly in the atypical lymphocytes. The granules varied in size and number from one or two detectable small granules to numerous coarse granules scattered throughout the cytoplasm (Fig. 1). This spectrum of size and number of granules was noted in all of the patients.

The five patients who were studied at days 5 or 7 exhibited decreases in total leukocyte counts from the initial evaluation. All but one of the patients (No. 9) showed a similar decrease in absolute lymphocyte counts. The percentage of atypical lymphocytes dropped slightly in all of the patients and lymphocytes with cytoplasmic granulation decreased in all but one patient (No. 7). The blood counts for the control subjects are shown in Table 2.

Cytochemistry

Moderate acid phosphatase activity was demonstrated in the cytoplasm of nearly all of the atypical lymphocytes of all the patients (Fig. 3). Occasional atypical lymphocytes showed marked positivity. Most of the lymphocytes exhibited minimal β-glucuronidase activity but some showed a strong focal or a moderate to marked diffuse reactivity. The atypical lymphocytes were mostly negative for the PAS and nonspecific esterase reactions. The cytochemistry of

Fig. 1. Downey type II atypical lymphocyte from a patient with IM. There is abundant clear cytoplasm with slight peripheral basophilia and coarse cytoplasmic azurophilic granules. Wright–Giemsa. × 660.

Fig. 2. Downey type III atypical lymphocyte from a patient with IM. There is basophilic cytoplasm, coarsely reticular nuclear chromatin, and a prominent nucleolus. Wright–Giemsa. × 660.

Fig. 3. Acid phosphatase activity in atypical lymphocyte from patient with IM. The distribution is diffuse and coarsely granular. Acid phosphatase. × 660.
Fig. 4. Electronmicrograph of peripheral blood lymphocyte from a patient with IM. There is abundant cytoplasm, large mitochondria, a prominent Golgi zone, numerous PTA (arrows), and a centriole (double arrows). Note the close approximation of the PTA to the centrosome region of the cell. Uranyl acetate, lead citrate. × 17,500.

Fig. 5. Electronmicrograph of peripheral blood lymphocyte from a patient with IM. There are four inclusions of PTA. Arrow points to inclusion with a 90° orientation of the bundles of tubular arrays. Uranyl acetate, lead citrate. × 35,000.
the atypical lymphocytes in the control subjects was similar to that of the patients.

**Ultrastructure**

Ultrastructurally, the lymphocytes which appeared to correspond to the atypical lymphocytes in the smears were medium to large, 5 to 8 μm in diameter. They contained abundant cytoplasm, moderately clumped nuclear chromatin, free ribosomes, occasional strands of rough endoplasmic reticulum, numerous large mitochondria, and a prominent Golgi apparatus (Fig. 4). The most striking ultrastructural feature of these cells was the presence of electron-dense tubular cytoplasmic inclusions. The structure of the inclusions was essentially similar in all the patients studied. The inclusions ranged in size from

![Fig. 6. Electronmicrograph of peripheral blood lymphocyte in E rosette from a patient with IM. Note PTA in the cytoplasm (arrows). Uranyl acetate, lead citrate. x 24,000. Inset: lower power of the same lymphocyte more clearly demonstrating the E-rosette formation. Uranyl acetate, lead citrate. x 5600.](image-url)
ATYPICAL LYMPHOCYTES IN IM

1000 to 6000 Å, were usually membrane bound, and consisted of parallel arrays of microtubule-like structures (Fig. 5). The tubules, 150-300 Å in diameter, were in bundles and packed in wall-to-wall contact with each other. The tubular bundles were often oriented at 90° to each other within the inclusion vacuoles. There was frequently an associated dense amorphous material.

These tubular inclusions, which we have previously referred to as PTA, were usually found in or near the centrosome region of the cell and had a close association with the centriole (Fig. 4). PTA were found in 15°-75° of the lymphocytes (Table 1). They were present in the atypical lymphocytes but not in the lymphocytes which corresponded to the nonatypical lymphocytes in the blood smears. Ultrastructural study of an E-rosette suspension in one of the patients demonstrated PTA in the lymphocytes binding sheep erythrocytes (Fig. 6). Of the patients studied at days 5 and 7, one (No. 4) showed a decrease by half in the percentage of lymphocytes containing PTA; the others manifested little change from the initial evaluation.

PTA were found in 5°-10° of the lymphocytes in the four control subjects (Table 2). This percentage of lymphocytes with PTA on ultrastructural study corresponded well with the number found in several other normal subjects studied in this laboratory and in other published reports.

Lymphocytes from the three patients studied for ultrastructural localization of acid phosphatase activity (Nos. 1, 3, and 7) exhibited activity in the Golgi area, lysosomes, and multivesicular bodies and within the membrane-bound PTA (Fig. 7). Not all PTA contained reaction product. Those that exhibited acid phosphatase activity always appeared to be membrane bound.

Fig. 7. Electronmicrograph of peripheral blood lymphocyte from a patient with IM. The presence of acid phosphatase reaction product (arrows) is depicted in the form of deposits in the Golgi cisterna and in the PTA. Uranyl acetate. x 18,000. Inset: high magnification electronmicrograph showing the localization of the acid phosphatase reaction product within a membrane-bound (arrows) inclusion of PTA. Uranyl acetate. x 43,000.
Surface Membrane Markers

There was an absolute increase in T lymphocytes which exceeded normal in all but two of the IM patients (Nos. 5 and 9) as determined by spontaneous binding of sheep erythrocytes. The range was 2500–10,400/cu mm (Table 1). B lymphocytes were slightly increased above the absolute normal range in two patients, one having an increased number of lymphocytes with surface immunoglobulin (patient 2) and one with increased lymphocytes bearing complement receptors (patient 7). The percentage cEA rosettes was 0.5%–2.5% in the five patients who had simultaneous cEA assays as controls for the cEAC′ assay. It is likely, therefore, that 12%–30% of the lymphocytes that bound cEAC′ in the patients did so as a function of Fc receptors rather than complement receptors. Zero to 2% of the normal subjects’ lymphocytes bound cEA. The number of lymphocytes bearing Fc receptors was increased above normal in five of the patients. At days 5 and 7, no consistent changes were noted in the percentage of lymphocytes exhibiting the various surface markers (Table 1). The results for the control subjects are shown in Table 2.

DISCUSSION

IM is a self-limited lymphoproliferative process characterized by increased numbers of atypical lymphocytes in the blood. The morphology of atypical lymphocytes may be variable, but in most cases of IM, the predominant cell is the Downey II reactive lymphocyte. In some patients, there is a small minority of Downey I and/or Downey III lymphocytes. Information from several studies1,4,6 indicates that the atypical lymphocytes in IM consist of a major population of T lymphocytes representing a host reaction to EBV-infected cells and a minor population of EBV-infected B lymphocytes. The T lymphocytes in IM have been shown to kill specifically EBV-genome-carrying B cells in vitro.22

In the present study, an absolute increase in T lymphocytes was demonstrated. The predominant morphologic pattern of the atypical lymphocytes in all of the patients was that of the Downey II lymphocyte. There was a minor population of the blastlike Downey III lymphocytes in some of the patients. It appears from our studies that the major population of atypical lymphocytes in IM, the Downey II cells, represents a T-lymphocyte expansion. It is possible that the minor morphologic population of atypical lymphocytes, the Downey III cells, corresponds to a population of lymphocytes transformed by the EBV.

Cytochemically, the atypical lymphocytes exhibited moderate to marked acid phosphatase activity and variable but sometimes moderate to marked β-glucuronidase activity. The activity of these enzymes has been reported to be increased in normal T lymphocytes23 and in certain T-lymphocyte lymphoproliferative disorders.24,25

Ultrastructural studies of the peripheral blood lymphocytes in our patients identified an increased number of lymphocytes with PTA. The PTA were found in lymphocytes corresponding to the predominant atypical lymphocytes in Wright’s stained smears. The same atypical lymphocytes frequently contained azurophilic granules on light microscopic examination. The distribution of PTA within the lymphocytes and their appearance in low-power electron microscopy appeared to correspond to the azurophilic granules. However, in
most of the patients the percentage of lymphocytes with azurophilic granulation exceeded the number of lymphocytes with demonstrable PTA. The number of cytoplasmic azurophilic granules was variable in the lymphocytes, some containing only one or two fine granules and others multiple coarse granules. The fact that fewer lymphocytes contained PTA ultrastructurally than azurophilic granules in light microscopy may in part be related to sampling error. A few small granules in a lymphocyte could be missed in one or two random sections of cell pellets, the lymphocyte thus appearing negative for PTA. It is also probable that the azurophilic granules within some of the lymphocytes represent other structures, such as lysosomes, on ultrastructural examination. In the atypical lymphocytes no structures other than PTA were identified ultrastructurally which could account for the azurophilic granules seen in light microscopy.

The PTA were found in the atypical lymphocytes, and therefore occurred predominantly, if not exclusively, in T lymphocytes in this group of patients. In the patient whose E-rosette suspension was studied ultrastructurally, PTA were identified in the lymphocytes which bound sheep erythrocytes (Fig. 6). Since 50%-78% of lymphocytes from normal controls type as T cells by E-rosette techniques in this laboratory, and 0-10% of lymphocytes from normals contain PTA, it was apparent that not all T lymphocytes contained PTA. The relatively low percentage of lymphocytes containing PTA in normal individuals and their occurrence in the Downey type II lymphocytes suggests that only a subset of T-lymphocytes contain PTA and that this subset is expanded in IM. An alternative possibility is that the PTA may be a transient finding in T lymphocytes, appearing in certain biologic states of the cell such as when the lymphocytes are activated and transformed. We have recently studied four patients with a chronic lymphoproliferative disorder, most closely resembling chronic lymphocytic leukemia, in which the proliferating lymphocytes manifested similar morphologic, ultrastructural, and membrane surface marker characteristics to the Downey type II atypical lymphocytes seen in IM. Greater than 75% of the lymphocytes from these four patients contained PTA. The lymphocytes in this disorder appeared to represent a sustained proliferation of T lymphocytes which corresponds to the transient and rapidly evolving population of lymphocytes in IM.

PTA have been identified in blood lymphocytes by several investigators. Hovig and associates first observed them in lymphocytes from a patient with rheumatoid arthritis and Huhn found them in 1%-5% of lymphocytes from 12 apparently healthy people. They have subsequently been identified in lymphocytes from patients with Chediak-Higashi syndrome, systemic and discoid lupus erythematosus, and sarcoidosis. They have been described as occurring in an increased number of blood lymphocytes in a patient with hairy cell leukemia, in patients with Wiskott-Aldrich syndrome, and in patients with Hodgkin disease. We have previously reported PTA in lymphocytes from patients with various hematologic diseases and in healthy individuals.

The origin and composition of PTA is unknown. Using cytochemical studies, Hovig and associates have shown that PTA do not contain RNA or DNA. White has suggested that they have their origin in the endoplasmic reticulum.
Bariety and associates\textsuperscript{29} have suggested that they arise from microtubular alteration of the mitochondria. Both White\textsuperscript{27} and Bariety and associates\textsuperscript{29} have noted the morphologic similarity of the inclusions to cytoplasmic microtubules. Our observations indicate that the PTA are usually found in the centrosome region of the cell and may arise from the centriole as some other microtubules do.\textsuperscript{9} Some may then become membrane bound and related to lysosomes; our demonstration of acid phosphatase activity within many of the PTA which were membrane bound (Fig. 7) lends support to this relationship. Whatever their function, PTA appear to represent a normal organelle occurring in certain populations of lymphocytes or occurring at a particular stage in the life cycle of lymphocytes.

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