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PROGRESS

Infectious Mononucleosis and Mononucleosis Syndromes

Clinical, Virological and Immunological Features

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Infectious mononucleosis (IM) and cytomegalovirus (CMV) mononucleosis are caused by a primary infection with related viruses, Epstein-Barr virus (EBV) and CMV. Despite the similarity of clinical manifestations, basic differences exist: (1) The heterophil antibody (HA) response is absent in CMV mononucleosis, whereas it is present in IM. (2) In IM atypical lymphocytosis reflects proliferation of B cells early and of T cells later in the disease course; in CMV mononucleosis the situation appears complex. (3) In blood, EBV is restricted to B lymphocytes, whereas CMV is found in polymorphonuclear and mononuclear leukocytes. (4) Complications of CMV mononucleosis such as hepatitis and pneumonitis may be due to virus cytopathic effect in target organs. Prominent tonsillopharyngitis with adenopathy, and visceral complications of IM are related to lymphoproliferation which is self-limited except in males with a rare familial defect in defense against EBV. Immune complex-mediated pathology may occur in both diseases. (5) CMV is frequently transmitted to a fetus in utero *or to an infant during or after birth, and this occasionally leads to severe cytomegalic inclusion disease; vertical transmission of EBV appears to be exceptional. (6) Secondary EBV infections are associated with certain malignancies whereas such an association has not been recognized in the case of CMV.*

Toxoplasma gondii is another cause of HA-negative mononucleosis. Its complications in the heart, in skeletal muscle and in the central nervous system are related to direct invasion by the parasite. Cellular immunity plays an important role in defense against all three agents.

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ABBREVIATIONS USED IN TEXT

CF = complement fixing
CMV = cytomegalovirus
EA = early antigen
EBNA = EBV-associated intranuclear antigen
EBV = Epstein-Barr virus
HA = heterophil antibody
IFA = indirect fluorescent antibody (test)
IHA = indirect hemagglutinating antibodies
IM = infectious mononucleosis
LFT = liver function test
MA = membrane antigen
NPC = nasopharyngeal carcinoma
VCA = virus capsid antigen

ACUTE FEBRILE DISEASES of adolescents and young adults accompanied by pronounced lymphocytic response are usually diagnosed as infectious mononucleosis (IM) or heterophil antibody (HA)-negative mononucleosis. IM is caused by a primary infection with Epstein-Barr virus (EBV).[1,2] HA-negative mononucleosis is due to EBV[3] or to cytomegalovirus (CMV)[4] and less commonly to Toxoplasma gondii;[5,6] beta-hemolytic streptococcus; Listeria monocytogenes; viruses such as adenovirus, hepatitis A, herpes simplex, rubella and mumps,[7] and reactions to para-aminosalicylic acid, diphenylhydantoin or isoniazid. Human herpesviruses including EBV and CMV,[8,9] and IM[10-12] have been extensively reviewed. This article deals with clinical, virological and immunological features of IM, CMV and toxoplasmic mononucleosis.

Infectious Mononucleosis

IM is an acute illness characterized by fever, pharyngitis, cervical lymphadenopathy, an absolute (greater than 4,000 per cu mm) and a relative (greater than 50 percent) increase of mononuclear cells in the peripheral blood, atypical lymphocytosis (greater than 20 percent of the total leukocyte count[13]) and abnormal findings on liver function tests (LFT). The differential HA test (Paul-Bunnell-Davidsohn test)[14] is positive in 90 percent of young adults with primary EBV infection.

Spectrum of EBV Infections[15]

In patients with IM, primary antibody response to EBV develops and thereafter immunity to IM is maintained for life. Typical IM develops when infection occurs in adolescence or young adulthood; in childhood most infections are subclinical or atypical. Among deprived socioeconomic groups, infection usually occurs in early childhood. Infection occurs in 12 percent of susceptible American and English freshman students, in 25 to 75 percent of whom IM develops.[16-19] The annual incidence of clinical IM is about 5 percent in susceptible students, but only one hundredth this figure in general population.

Secondary attack rate of IM in college roommates is about 5 percent[12] whereas, in well-to-do Swedish families, it was shown to be 33 percent.[20] The incubation period has been recorded at 30 to 45 days.[21] EBV is transmitted in saliva (IM is known as a "kissing disease"). Acquisition of IM without a known contact is explained by prolonged oropharyngeal excretion of EBV.[22-25]

Secondary EBV infections are associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and possibly with the lymphocyte-depletion and mixed cellularity types of Hodgkin's disease.[26] Although the role of EBV in these malignancies is controversial, recent evidence suggests a causative rather than a passenger role.[26-32] The course of EBV infection may depend on the genetic susceptibility of the host,[33-36] the status of humoral and cellular immunity at the time of primary infection,[35,36] coexistent malaria,[37] an endogenous ribonucleic acid (RNA) tumor virus,[38] or involvement of virulent virus strains.[39-41] Susceptibility to IM is not linked to specific HL-A types;[42] however, increased frequency of HL-A2 at the first locus and a new antigen Singapore-2 at the second locus are associated with nasopharyngeal carcinoma.[43]

Manifestations and Laboratory Features

Following nonspecific prodromes the presenting symptoms are fever and sore throat which persist two weeks or more and are unresponsive to antibiotic therapy; lympadenopathy, jaundice or a transient maculopapular rash are less common presentations. Pharyngeal exudate is present in about half and streptococcal superinfection in a quarter of cases. Petechial enanthema on the soft palate is common. Lymphadenopathy lasting several weeks is a constant feature and involves posterior cervical nodes or is generalized. Splenomegaly and hepatomegaly are frequently present and in most patients findings on liver function tests are abnormal.[44] Involvement of the lymphoreticular system may cause abdominal pain. Atypical lymphocytes ("Downey" cells[45]) have been classified as: Type I—about the size of small lymphocyte with clumped chromatin and sharply defined parachromatin; Type II—larger cell with "smudged" chromatin; Type III—large

cell with royal blue cytoplasm, open chromatin and a prominent nucleolus.

In children EBV infection should be suspected when a febrile illness is accompanied by atypical lymphocytosis (absolute lymphocytosis with 3 to 10 percent atypical lymphocytes is normal before the age of 6), lymphadenopathy, and splenomegaly or hepatomegaly, often without an HA response.[46] Severe complications, including Reye's syndrome, may occasionally occur in the absence of typical features of IM. A high antibody titer to virus capsid antigen (VCA) and a low complement-fixing (CF) antibody titer supports the diagnosis of a primary EBV infection in childhood.[47] In young adults, the ratio of clinically manifest (including respiratory symptoms only) to subclinical disease is about 2 to 1.[19] The disease is rare in middle age but tends to be severe. Symptoms may recur in patients responding late to the restricted (R) component of the early antigen (EA) complex.[48]

Complications

IM is usually a benign illness. The most frequent complication has been hypersensitivity following treatment with ampicillin or penicillin (95 percent and 44 percent, respectively, of those receiving the drugs[49]), as a maculopapular rash which is of greater severity than the "spontaneous" rash. This reaction does not imply permanent hypersensitivity to either drug.[49-52]

Hemolytic anemia occurs in rare instances one to two weeks after the onset of IM and is thought to be due to anti-i agglutinin (rarely anti-N agglutinin[53]) in a high titer[54] and active over a wide thermal range.[55,56] Red cells may be converted from the adult I antigenic form to the fetal i form.[53,57] Cold agglutinins are usually IgM but IgG agglutinins[58] may be found which act in conjunction with a cold-reactive IgM antibody against IgG.[59,60] The direct Coombs test may be positive using antiglobulin, anti-C3 or anti-C4 reagents. Anemia is usually due to extravascular hemolysis but intravascular hemolysis may occur in severe cases.[53,61] Patients with spherocytosis, thalassemia or congenital pyruvate kinase deficiency develop increased hemolysis during stress including IM.[62] Some IM patients have increased autohemolysis which correlates with spherocytosis and elevated mean corpuscular hemoglobin concentration suggesting occult hemolysis.[63] Hypersplenism of chronic infection[64] or bone marrow depression[53] may be seen.

Although thrombocytopenia and abnormalities of platelet function are common, thrombocytopenic purpura is rare. Antiplatelet antibodies[65] and anti-i agglutinins (platelets carry the i-antigen)[66] appear to be of pathogenic significance. In some patients disseminated intravascular coagulation with hypofibrinogenemia may contribute to bleeding.[67] IM presenting with lymphopenia is exceptional and tends to have severe complications.[68] Severe neutropenia,[69-71] and very rarely pancytopenia,[72] may arise several weeks after the onset of IM. Neutrophils have low alkaline phosphatase content during the first week of illness.[69]

Lymphocytic infiltration results in visceral complications. The prognosis in carditis[73,74] and most other complications is generally good but rupture of the spleen; neurological complications; respiratory obstruction; lymphoproliferative or pancytopenic disorders, and secondary hypergammaglobulinemia or agammaglobulinemia may be fatal.[75-77] Acute nephritis occurs in as many as 13 percent of patients[78] in the form of either an interstitial nephritis with tubular atrophy or a mesangial proliferative glomerulonephritis. Interstitial mononuclear infiltrates distinguish mononucleosis from poststreptococcal nephritis.[79] Hemolytic uremic syndrome followed IM in one 14-year-old boy.[80]

Hepatitis is mild and the abnormalities on LFT's reflect the degree of infiltration of portal tracts by mononuclear cells and of hepatocyte necrosis.[81] Intense hyperbilirubinemia may result from a combination of hepatitis and hemolytic anemia.[82] Fatal hepatic necrosis is rare.[83,84] The ultrastructure of liver cells in hepatitis shows dilation of the endoplasmic reticulum[85] and, in the presence of hepatic necrosis, margination of chromatin and herpes-like virions.[84] A transient malabsorption is associated with thickened jejunal folds, which are infiltrated with large lymphocytes.[86] Diabetes mellitus may have a fulminant onset during IM.[87] Upper respiratory obstruction is a serious complication.[88] Interstitial lung infiltrates may be followed by Hemophilus influenzae or Staphylococcus aureus superinfection, pleural effusion,[89] or septicemic features.[90]

Neurological complications include encephalitis[91] occasionally with focal manifestations,[92] acute cerebellar syndrome,[93] aseptic meningitis, Guillain-Barré syndrome,[94] transverse myelitis, asymmetrical brachial neuropathy (mononeuritis, mononeuritis multiplex,[95] neuralgic amyotrophy —shoulder-girdle syndrome—or radiculopathy),

Bell palsy,[96] and Reye syndrome.[97,98] The incidence of neurological complications is less than 1 percent[99,100] and these may occur at any time, but usually one to three weeks after onset of IM.[101] Atypical lymphocytes, HA and EBV antibody in the spinal fluid[93] suggest that the virus directly involves the nervous system but a demyelinating process also occurs.[92] In one study, a third of young patients with Guillain-Barré syndrome and a third with Bell palsy were associated with a recent primary EBV infection, although they were without clinical signs of IM or HA response.[102] Chorioretinitis has been reported in a few cases.[103]

The relationship, if any, among lymphoma, leukemia and EBV is not clear.[104-112] In one 16-year-old boy a mononucleosis-like illness progressed to a fatal generalized lymphoproliferative disorder of B-type. EBV infection was shown to be present by the finding of herpes virions in

TABLE 1.—*Serological Findings in Two Types of Mononucleosis*

	Infectious Mononucleosis		*CMV Mononucleosis*	
	Finding	*Reference*	*Finding*	*Reference*
Antibodies				
Heterophil	Rise (90% of adults, uncommon in children)	(2,128)	None	(3,182)
to Epstein-Barr virus (EBV) capsid antigen (IgG antibody) (measured by immunofluorescence [289] or radioimmunoassay [290])	High, rising or falling titer of antibody	(128)	No change; except in rare dual infections	(3,182)
to EBV capsid antigen (IgM antibody)	High, and after 2-3 months falling titer	(126)	Weak cross-reaction	(127)
to EBV early antigen (EA) (including responses to diffuse [D] and restricted [R] type antigens)	Rise of antibodies to diffuse antigens (in 70-80% patients)	(128,291)	?	
	rise of antibodies to restricted antigens in 16%	(48)	?	
EBV complement-fixing (CF)	Late rise (7th month after onset)	(130,131)	?	
to EBV nuclear antigen (EBNA)	Late rise (1-6 months post onset)	(29,128)	?	
EBV neutralizing	Early rise	(292)	?	
Cytomegalovirus (CMV) complement-fixing	No change	(3,184)		
	(except in rare dual infections)	(185,223)	Rise (peak 4 to 7 weeks after onset)	(3,4)
to CMV intracellular antigens (IgG antibody detected by immunofluorescence)	No change	(128)	High or rising titer	(184)
to CMV intracellular antigens (IgM antibody detected by immunofluorescence)	Extensive cross reactions	(240)	Present at least 2 to 8 months	(192,241)
	(some due to rheumatoid factor)	(241)		
to CMV soluble antigens (indirect hemagglutinating antibody)	?		Rising titer	(236)
CMV neutralizing	Rise (test done in presence of complement)	(244)	Rising titer	(4,244)
to CMV early antigen	?		Antibody rise (peak 10 to 19 days after onset)	(246)
to CMV nucleocapsid	.....	....	Antibody rise (1 to 2 weeks post onset)	(245)
to CMV enveloped virions	.....	....	Antibody rise (4 to 6 weeks post onset)	(245)

lymph nodes, EBV deoxyribonucleic acid (DNA) in the spleen and by HA. There was failure to produce antibody to EBV in the patient and leukocytes were not stimulated by phytohemagglutinins. Three male relatives died from a similar disorder.[113] In another family, three males had an acute illness with adenopathy and hepatosplenomegaly which was fatal in one patient, whereas in the other two agammaglobulinemia developed.[114] In a third kindred, six of 19 boys died of a disorder characterized by proliferation of lymphocytes and histiocytes, either hyper- or agammaglobulinemia, and by certain features of IM.[77]

Differential Diagnosis

The following are differential diagnoses:

- HA-negative mononucleosis;
- The exudative pharyngitis caused by bacterial or other viral pathogens, or occurring in acute leukemia;
- Pronounced lymphocytosis accompanying pertussis and acute infectious lymphocytosis; moderate lymphocytosis in certain chronic bacterial and in many acute viral infections;
- Prodromal arthralgia, skin rash and elevated serum transaminase and bilirubin of hepatitis A and B (serum transaminase and bilirubin levels are higher in viral hepatitis than in IM;[115] alkaline phosphatase is elevated in both diseases, but in patients with IM there is a dissociation between elevated alkaline phosphatase and serum glutamic oxaloacetic transaminase, and a low bilirubin level[116]);
- Systemic diseases, infective endocarditis, lymphoma and acute leukemia resemble the "typhoid" course of IM.

Serology and Immunopathology

Serological and immunologic findings are shown in Tables 1 and 2.

HA agglutinating sheep red cells are found in patients with IM at a titer of 1:112 or greater whereas usually low titers occur in cases of malignant lymphomas, sarcoidosis,[117] rheumatoid arthritis,[118] viral respiratory infections and serum sickness. The differential HA test is specific for IM when the titer is decreased 8-fold or less by absorption with guinea pig kidney but decreased 16-fold or more following absorption with beef erythrocytes.[14] Horse erythrocytes allow a sharp differentiation between IM agglutinins and non-

TABLE 2.—*Immunologic Aberrations in Infectious and Cytomegalovirus Mononucleosis*

	Estimated Incidence (Infectious Mononucleosis) Percent*	*Reference*
Auto- and isoantibodies		
Cold agglutinins (usually with anti-i specificity)	8- 79	(54,202)
Rheumatoid factors		
a. warm-reactive	10	
b. cold-reactive	72	(293)
Antinuclear antibodies (transient)	66	(294)
Cryoglobulins (transient, mixed IgG and IgM)	95	(295)
Venereal Disease Research Laboratories test (biological false positive)	19	(294,295)
Donath-Landsteiner haemolysin	?	(140)
Antilymphocyte	100	(142-144)
Antiplatelet	?	(65)
Antismooth muscle	44- 81	(141)
Antimicrotubules	81	(145)

	Infectious Mononucleosis	*Reference*	*Cytomegalovirus Mononucleosis*	*Reference*
Lymphocytes				
Atypical lymphocytes in peripheral blood	B lymphocytes elevated for 1-3 weeks (max. 1st week); T lymphocytes elevated for 5 weeks (max. 2nd week)	(150)	Atypical lymphocytes elevated for weeks to months	(4)
			T cells increased	(148)
			or nul cells increased	(185)
Immunosuppression				
of humoral immunity	?	....	in one case	(185)
of cellular immunity	100 percent	(150)	in one case	(185)

*The incidence in cytomegalovirus mononucleosis is not known precisely.

IM agglutinins (which are reduced equally or to a greater degree by absorption with guinea pig kidney than with beef red cells).[119] The slide agglutination test[120] using citrated horse erythrocytes has optimum sensitivity whereas a beef hemolysin test appears the most specific.[121] It is not clear whether HA arises as a response to common antigens on sheep erythrocytes and EBV-transformed cells,[122] or through another mechanism.[123]

Antibodies appear in the following sequence: (1) In the incubation period, IgM and IgG antibodies to VCA and EA; (2) in the acute phase, EBV neutralizing antibodies and antibodies to membrane antigen (MA), and HA; (3) in the convalescent phase, antibodies to CF antigen and to EBV-associated intranuclear antigen (EBNA). The following findings are characteristic of IM:

- IgM antibody to EBV;[124-126]
- IgG antibody to VCA in a titer of at least 1:320, or a rising or falling titer;
- Transitory response to the diffuse (D) component of the EA complex (present in 85 percent of patients);[127] 15 percent of patients respond in late convalescence with anti-R (restricted component) antibodies and tend to have a complicated course;[48]
- Late rise of CF and anti-EBNA antibodies;[127-131]
- Isolation of EBV from the throat indicates either a recent or a remote infection;[23,132]
- Peripheral leukocytes from patients with IM rapidly establish permanent lines *in vitro*[133] (*in vivo* some EBV exists in a nonproductive state[134]); EBNA is found in about 1 percent of peripheral B lymphocytes [Jondal, M., personal communication]).

IgM, IgG, IgA[135] and, in some patients, IgE and IgD[136] immunoglobulins are elevated by as much as 100 percent, yet less than 5 percent can be accounted for by HA or anti-i antibody.[137] Iso- and autoantibodies in IM include: cold agglutinins, rheumatoid factor, antinuclear factor,[138] Wasserman antibody, Donath-Lansteiner cold hemolysin,[139] and antibodies to erythrocytes, platelets, smooth muscle,[140] lymphocytes,[141] subpopulations of T- and B- lymphocytes[142,143] and cytoplasmic microtubules.[144] IgM-IgG cryoglobulins may contain some of these antibodies[145] in addition to EBV VCA antibody, virions and components of the classical and alternative complement pathways.[146]

The atypical lymphocyte has been thought to be of T-cell origin.[147-149] Findings in recent studies suggest that B-cells proliferate mainly during the first week of illness whereas T-cells do so thereafter.[150-152] This may result from an initial viral invasion of B-cells (*in vitro* EBV grows only in B-cells[153-156]), induction of viral antigens in B-cells and a subsequent cytotoxic response by T-lymphocytes.[149,150,157-163] Antibodies to EBV MA may also control lymphoproliferation.[164] During IM there is depressed lymphocyte response to various mitogenic and antigenic stimuli, and dermal anergy.[150] The depression may result from suppression of responder T-cells by suppressor T-cells or as a result of responder cells releasing a negative mediator.[165,166]

Histopathological changes in lymph nodes involve a mixed proliferation of small and large lymphocytes, plasma cells, "immunoblasts" (large cells with sharply demarcated nuclei containing loose chromatin and two nucleoli, and a pyroninophilic cytoplasm) and blood vessels. Binucleate "immunoblasts" resemble Reed-Sternberg cells and may lead to an erroneous diagnosis of Hodgkin disease.[167] In more advanced stages distortion of normal architecture with lymphoid infiltration of the capsule is found.[167-169] Atypical lymphocytes infiltrate the spleen, especially in the red pulp and sinusoids. The follicles contain eosinophilic material which includes damaged arterioles plus exuded proteins.[170] In the sternal bone marrow, pronounced hyperplasia may simulate malignant transformation.[171]

Treatment

Treatment of uncomplicated IM is symptomatic. Most patients recover in five weeks or less. Orally given prednisone or intravenously given hydrocortisone is indicated for severe respiratory or central nervous system involvement, thrombocytopenic purpura with hemorrhage, hemolytic anemia or severe hepatitis.[172,173] Splenectomy has occasionally been required for treatment of steroid-resistant thrombocytopenia.[174] Transfusions should be administered at 37°C to avoid cold agglutination.

Cytomegalovirus Mononucleosis

CMV mononucleosis, which is caused by a primary CMV infection, has many features similar to IM but there is no HA response. It occurs either "spontaneously" (CMV may be transmitted by oral route or venereal contact[175]) or after blood transfusion.

Epidemiology

In childhood, subclinical and minor respiratory, gastrointestinal and hepatitic forms of CMV infection are common.[176,177] Typical CMV mononucleosis occurs in subjects over 20 years of age.[176,178,179] CMV antibody is acquired at an earlier age in subjects of low-economic status.[180-182] There are also geographical differences. In Japan subclinical infection occurs in 60 percent of infants by 5 months of age.[183] Among 200 Finnish patients with mononucleosis, CMV was associated with 19 of 44 heterophile-negative cases.[3] Among 411 Swedish patients with mononucleosis, CMV was involved in approximately 20 of 300 HA-negative illnesses. In four patients there were dual CMV and EBV antibody rises.[184] The transmission of CMV depends on prolonged shedding of virus in the throat,[176,185] or in the urogenital tract including semen.[186,187] Postransfusion mononucleosis may occur at any age. The incubation period is one to three months. The following is relevant to virus transmission during transfusion and cardiopulmonary bypass:

- The risk of seroconversion is related to the volume of transfused blood but not to the level of preexisting CF antibody;[188]
- CMV had been found in cultured leukocytes of certain healthy blood donors[187] although subsequent studies[190,191] have not confirmed this;
- Some cases of posttransfusion mononucleosis result from a primary infection[192] whereas reactivation of a latent infection is thought to occur when there is evidence of a previous CMV infection;[193] the stress imposed by cardiopulmonary bypass may facilitate reactivation of a chronic infection.[194]

Clinical and Laboratory Features

Finnish patients with "spontaneous"[4] and posttransfusion CMV mononucleosis[195] had fever for two to five weeks, minimal or absent tonsillopharyngitis, and adenopathy. Initial leukopenia was followed by lymphocytosis with abundant atypical lymphocytosis which persisted for at least two weeks. Mild abnormalities on LFT's and, in a few patients, hepatomegaly, vestibular and cochlear involvement, arthralgia, skin rash, pneumonia and cold agglutinins were also found.[196] Some Swedish patients had conjunctivitis, vaginitis, severe headache and abdominal pains.[178] All of nine American patients[197] had prolonged fever, fatigue, myalgia and mild sore throat; two had generalized lymphadenopathy and three splenomegaly. In one patient Guillain-Barré syndrome developed and in another splenic infarction. Fever relapsing over many months was a particular feature in German patients.[198]

Complications

Ampicillin-induced skin rash,[199] hepatitis and polyneuritis are the most frequent complications of CMV mononucleosis in normal subjects. Less common complications include congenital disease in the offspring,[200] endometritis,[201] thrombocytopenia, hemolytic anemia,[202] interstitial pneumonitis,[203] myocarditis and pericarditis,[204] inflammation of pancreatic islets,[205] acute onset diabetes,[206] epidermolysis[207] and meningoencephalitis.[208] In immunologically impaired patients, CMV has been related more often to severe manifestations than in normal subjects,[209] including high spiking fever, arthralgias, pneumonitis, hepatitis and retinitis.[210-212]

Factors determining virus transmission and pathogenicity in the fetus are poorly understood. Congenital CMV infection is common (0.5 to 1.5 percent incidence[213]), but in most cases patients are asymptomatic at birth. There is a high level of immunity and of cervical shedding of CMV in women of childbearing age in some communities (in Alabama 89 percent of women had antibody and 11.3 percent shed virus during the third trimester).[214] Also some mothers have consecutive congenitally infected infants.[215] These findings suggest that primary gestational infections cannot explain all congenital infections. It is, however, conceivable that the severe congenital disease results from primary maternal infection in the first[200] or second[216,217] trimester.

Hematological complications of CMV mononucleosis include hemolytic anemia[202] and thrombocytopenia.[218,219] Thrombocytopenia may be severe and not respond well to splenectomy or to steroids.

Although mild liver involvement is common, severe hepatitis due to CMV is rare.[185,220,221] Findings on liver biopsy show periportal mononuclear or mixed cell infiltrates occasionally accompanied by Kupffer cell hyperplasia and focal necrosis of liver cells. Inclusion-bearing hepatocytes[222] and bile stasis[84] are also found. Rarely cholestatic jaundice with substantial elevation of bilirubin and alkaline phosphatase and with liver granulomas is found.[223]

CMV infection was associated with acute inflammatory disorders of the central nervous system in

two Finnish patients[224] and of the peripheral nervous system in English patients.[206] CMV was incriminated in more than a third of 80 American cases of acute polyneuritis.[225] Vestibular and cochlear involvement may occur in CMV mononucleosis.[4] Although most complications are benign, in one patient myocarditis, encephalitis, hepatitis and adrenal insufficiency developed and the patient died from congestive heart failure.[226] In another, carditis and hepatitis were followed by disseminated intravascular coagulation and shock.[227]

Immunopathology

Immunologic findings are shown in Table 2.

Cold agglutinins, rheumatoid factor, antinuclear antibodies, mixed IgM and IgG cryoglobulins (rich in antinuclear antibodies, rheumatoid factor or cold agglutinins),[146] and erythrocyte autoantibodies may develop in mononucleosis.[202] In a patient with acute leukemia, CMV mononucleosis and a transient monoclonal gammopathy of IgA-lambda type developed.[228] It is conceivable that arthralgia[196,212] and glomerulitis[229] in infected patients result from deposition of immune complexes. Some cases of hemolytic anemia could be a consequence of occult infection of the reticuloendothelial system.[230] The origin of atypical lymphocytes is not clear but, in one case of CMV mononucleosis, increased numbers of T-cells were found,[148] whereas, in another case, increased null cells were observed.[185]

Serology

Table 1 shows serologic findings.

With the use of a broadly reactive CF antigen from the strain AD 169, antibody response is detected in nearly all primary CMV infections except in infants.[231-233] This antibody is specific[234] and is largely of the IgG class. In some infected subjects,[212,235] the titer of antibody may have declined below 1:8 at the time of reinfection giving an impression of a primary infection. Indirect hemagglutinating antibodies (IHA) of IgM and IgG classes[236] rise earlier and to higher titers than CF antibodies. Immunofluorescent IgG antibody titers generally parallel those of IHA. Neutralizing antibody is slow to appear,[237] and displays strain specificity.[238,239] Immunofluorescent IgM antibody is found in recent infections.[192,240-242] False-positive IgM reactions may result when IgM rheumatoid factor-like antibodies attach to antibodies of the IgG class. This can be circumvented by preabsorbing the serum with aggregated gamma globulin.[243] Antibodies determined by complement fixation tests using enveloped virions develop several weeks later than those reacting with nucleocapsids.[244,245] Immunofluorescent antibody to an early antigen (EA) peaks later than the immunofluorescent IgG antibody and is absent from sera of healthy subjects seropositive in the CF test.[246]

Cytomegalovirus Viremia and Excretion

In viremic blood, infectious CMV is carried predominantly in polymorphonuclear leukocytes and, at low titer, in the mononuclear leukocyte fraction[202] where it may reside in monocytes (Fiala, M. and Saxon, A., unpublished). Mouse CMV is associated with B-lymphocytes in both latent and productive infections.[247] A lymphoblastoid line derived from peripheral leukocytes of a child congenitally infected with CMV is persistently infected with EBV and CMV.[248] B-cell lines carrying EBV can be abortively superinfected with CMV.[249] CMV stimulates host-cell deoxyribonucleic acid (DNA) synthesis in permissive as well as nonpermissive cells[250] and transforms hamster embryo fibroblasts.[251] In man, CMV viremia may be transitory when it results from phagocytosis of virus by polymorphonuclear leukocytes or monocytes, or both; or it could represent a stable association of virus with lymphocytes with a possibility of oncogenic interactions.

Treatment and Prophylaxis of Cytomegalovirus Infections

No specific therapy is usually indicated. Experimental treatment with adenine arabinoside[252] resulted in a temporary decrease of CMV excretion without any effect on the clinical course.[253] An experimental live vaccine is immunogenic in man,[254] but it is of unproven value at present.

Toxoplasmic Mononucleosis

Toxoplasmosis—Clinical Spectrum

Infection with the protozoan parasite Toxoplasma gondii may be asymptomatic (most cases) or cause a variety of manifestations. The most common feature of postnatal infection is lymphadenopathy, in some cases associated with fatigue, malaise, fever, hepatomegaly, splenomegaly, lymphocytosis and the presence of atypical lymphocytes. The HA test is negative and specific serologic tests for toxoplasmosis are positive. Congenital infection may occur when the mother

acquires the disease during pregnancy. Chronic toxoplasmosis may cause retinochoroiditis.

Etiology and Epidemiology

Toxoplasma is now classified among the coccidian parasites.[255] The organism has been recovered from a wide variety of mammals and birds, but one phase of its complex life cycle is unique to cats and other felids. In cats, intestinal epithelial cells are parasitized by asexual and sexual forms and oocysts are excreted in the feces. Oocysts become infective within one to several days after they are shed. Humans are incapable of developing the intestinal infection but harbor two forms of the parasite, the proliferative form (endozoite, tachyzoite) and the tissue cyst. The proliferative form is ovoid with a slightly tapered anterior end and measures 4 to 7 μ by 2 to 4 μ. It is able to penetrate and multiply in nearly all types of nucleated cells. Reproduction occurs by endodyogeny;[256] that is, the development of two daughter cells within the parent cell. The tissue cyst (30 to 60 μ in diameter) has a thin wall and may contain more than 3,000 individual organisms (cytozoites, bradyzoites).

Toxoplasma cysts have been demonstrated in mutton, pork and beef,[257] and clinical disease[258] and seroconversion[259] have been shown to follow the ingestion of raw and inadequately cooked meat. Domestic cats appear to be a major source of human infection.[260,261] Oocysts from cat feces are highly infectious and, under favorable conditions, may remain viable for many months to years. The prevalence of toxoplasmic antibody in humans is greater in warm, moist climates than in colder, dry areas and increases with age.[262] Approximately a fifth of young American adults are seropositive. Transmission has also occurred by accidental inoculation in the laboratory,[263] by organ transplantation[264] and by blood transfusion.[265]

Manifestations

The incubation period is estimated at 8 to 13 days for infections acquired by meat ingestion,[258] and 3 to 10 days for infections acquired in the laboratory.[263] Asymptomatic lymph node enlargement is the most common manifestation of acquired toxoplasmosis.[266,267] The lymph nodes of the head and neck are most frequently involved but generalized adenopathy occurs. A series of 38 patients with acquired toxoplasmosis[268] were found to have the following symptoms: lymphadenopathy (90 percent of patients), fatigue and malaise (40 percent), fever (37 percent), sore throat (21 percent), headache (18 percent), symptoms of myocardial disease (11 percent), retinochoroiditis (5 percent) and seizures (2.5 percent). Physical findings showed lymphadenopathy, usually posterior cervical nodes (97 percent), splenomegaly (32 percent), nontender hepatomegaly (32 percent), a maculopapular rash (11 percent) and erythema of the pharynx (8 percent). Atypical lymphocytes were present in 20 percent of the patients. The rash is maculopapular, nonpruritic and generalized, but usually spares the palms, soles and scalp. Dramatic cutaneous manifestations resembling a rickettsial infection are rare.[269]

Complications

Lymphadenitis usually resolves spontaneously over a period of weeks to months. Myocarditis, pericarditis,[270,272] pneumonitis[270] or myositis[273,275] may occur if the strain of parasite is particularly virulent or the immunologic responsiveness of the patient is impaired. Hepatitis,[276] glomerulonephritis[277] and interstitial nephritis[278] have been reported. In patients with impaired immunity, toxoplasmosis may cause severe central nervous system disease, encephalitis or a mass lesion, and myocardial and pulmonary invasion.[279-281]

Differential Diagnosis

Toxoplasmosis should be considered in the HA-negative mononucleosis syndrome. Lymphadenopathic toxoplasmosis may also mimic various forms of lymphoma. Central nervous system toxoplasmosis must be differentiated from disease due to other infectious agents, hemorrhage, cerebral or dural tumor, and progressive multifocal leukoencephalopathy.

Immunopathology

Cellular immunity appears necessary for complete protection of the host.[282] Corticosteroids, which suppress cellular defense mechanisms, predispose to infection. The lymphadenopathy of toxoplasmosis is attributed to hyperplasia of lymphoid tissue as part of the immune response.[283] Hypersensitivity of the delayed type results in necrosis in the vicinity of ruptured Toxoplasma cysts. Renal involvement may be due to immune complex nephritis.[277]

Diagnosis and Serology

Toxoplasma organisms may be recovered from infected tissue and body fluids by animal inocula-

tion or by tissue culture,[284] and may be shown to be present in tissue sections or impression smears by stains and by immunofluorescence. Histopathology of lymph nodes is diagnostic.[285]

The Sabin-Feldman methylene blue dye test[286] is specific and sensitive and has remained the reference standard for newer tests. Other useful serologic tests are the indirect hemagglutination test, the indirect fluorescent antibody test (IFA) and the complement fixation test.[284] Dye test antibody becomes detectable within one to two weeks after infection and the indirect hemagglutination test two to three weeks after infection, and both tests remain positive for life. The CF test is of value in determining the stage of infection as it becomes positive much later than the dye test. The IFA correlates well with the dye test, but false-positive reactions have been noted in the presence of antinuclear antibody.[284] Antibodies of the IgM class are detected by immunofluorescence (IgM-IFA test).[279-287] Acute infection is suspected when the IgM-IFA test becomes positive, even at low titer, and a dye test or IFA test has a titer of 1:1,000 or greater in a patient with compatible clinical manifestations. Acute infection is confirmed by IgM-IFA test of 1:600 or greater and a dye test or IFA test of 1:16,000 or greater.

Treatment

Toxoplasmosis without systemic involvement requires no treatment. Complications of toxoplasmosis may be treated with the combination of pyrimethamine and sulfonamides. Folinic acid and yeast will prevent the hematopoietic toxicity associated with pyrimethamine.[288]

Addendum

Since the termination of the literature search in February 1976, several important contributions have been reported. EBV in oral secretions has been found to be cell free and probably replicated in the parotid gland.[296] In Uganda, neonatal or perinatal infections with EBV, together with a heavy malaria burden or other stresses in early life, might be important determinants in the pathogenesis of Burkitt lymphoma.[297] EBV has been associated with encephalitis, in some cases even in the absence of heterophil response, by the titers of EBV antibodies.[298] Under crowded conditions, EBV may cause an outbreak of IM.[299] Elderly patients with IM tend to have a severe course with pronounced liver involvement.[300] The role of CMV in granulomatous hepatitis with lymphocytosis has been confirmed in two adults.[301] Murine CMV has frequently been used as a model of human infection. Thrombocytopenia occurs in both infections. Lymphoid cell necrosis, thymic atrophy, growth retardation and immune deficiency have been shown to occur in infected newborn mice.[302] Recently a primary CMV infection during the period after renal transplantation has been suggested as a possible factor in severe opportunistic infections of renal allograft recipients.[303] With the realization of CMV-associated morbidity in transplant patients, there is a renewed interest in the development of a CMV vaccine.

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Drugs and Diet as Causes of Vascular Headache

The first thing I'm interested in when I treat a patient with repetitive vascular headache is to find out if there's something that can be stopped, rather than something that I have to start therapeutically. . . . The first thing I'm sure to look for, and most of these patients are women, is whether or not they're receiving some type of estrogen treatment. . . . The majority taking birth control pills will have an increase in headache if they have a predisposition to vascular headache. This was more of a problem with the high-dosage forms of estrogen that were earlier available and they're less of a problem now; but they continue to be a problem. I know of no birth control pill on the market which is safe from the point of view of not aggravating migraine and occasionally producing stroke. . . . One can say exactly the same thing for postmenopausal replacement therapy. There are other drugs . . . that seem to be capable of aggravating vascular headache. The whole amphetamine group and, in some instances, the antihistamines are culprits. . . . There are clearly some patients in whom headache develops from dietary factors. The two common ones are the nitrites used to redden hot dogs, and tyramine. Now whether you go on from there to eliminate all milk products from the diet . . . remains to be examined, and I'm not sure that that has any real value. I'm more impressed by the common relationship of so-called functional hypoglycemia to migraine. If one wants to study migraine and precipitate an attack in a susceptible person, the best thing to do is to fast them all night and then give them a glucose tolerance test; and after about five or six hours, they'll get a lovely migraine headache for you as they get into a reactive type of hypoglycemia. If patients are instructed to reduce the amount of carbohydrate in their diet and to eat more lipid and protein and to stay away from starchy foods, they may experience a modest reduction in the frequency of headache. . . . I'm absolutely convinced that mild degrees of hypertension can be another important cause of vascular headache. . . . Patients with any kind of chronic pain, including intractable headache, tend to become depressed; and often, the only subtle symptom pointing to depression is early wakening in the morning with inability to get back to sleep. The trial of these patients on imipramine hydrochloride (Tofranil®) or amitriptyline hydrochloride (Elavil®) for periods of time in sizable doses, 25, 50 or 75 mg at bedtime once a day over weeks or months will result in considerable improvement in vascular headache.

—STANLEY VAN DEN NOORT, MD, *Irvine, CA*

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