Infections Associated with Immunologic Deficiency Diseases

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Efforts to understand why a young patient had repeated infections with common bacterial agents led eventually to our current understanding of the immune system. A brief review of the clinical and laboratory aspects of the major categories of *congenital* immune deficiency will provide the background for anticipating and managing infections in the patient with acquired immune deficiencies. First we will review the typical clinical and laboratory findings which should suggest that a patient may have one of the various forms of congenital immune deficiency, and then we will describe the patient with acquired immunodeficiency, the result of malignant disease or treatment with immunosuppressive agents or both. What kind of infection is such a patient likely to have, what is its course, and how can it be diagnosed and treated?

CONGENITAL IMMUNE DEFICIENCY

Bruton's Agammaglobulinemia

Bruton[7] in 1952 described an 8 year old boy who had been hospitalized 19 times for treatment of sepsis. During 10 of these illnesses, blood cultures were positive for pneumococci; types 33 and 6 were each responsible for 2 episodes. In addition, the child had repeated bouts of bacterial pneumonia, otitis, and cervical adenitis, all of which ran a prolonged course even with antibiotic therapy. Interestingly the child managed rubeola and varicella with no particular difficulty. The administration of polyvalent pneumococcal polysaccharide led neither to a decrease in the frequency of infections nor to the development of specific antipneumococcal antibody. An unusual plan of treatment was developed for this child: whenever he presented at the clinic with chills, fever and signs of infection, a blood culture was taken and penicillin was administered through the same needle. Eventually the child's serum proteins

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were studied and a deficiency of gamma globulin was demonstrated by electrophoresis. The child improved following treatment with periodic injections of pooled human gamma globulin and is alive and doing well today.

Patients with Bruton type of agammaglobulinemia, or sex-linked agammaglobulinemia as it is also called, lack the ability to make antibodies but have intact cell-mediated immunity. They have repeated infections with the common pyogenic bacteria, such as pneumococci, *Haemophilus influenzae,* streptococci, or pseudomonas, but can demonstrate delayed hypersensitivity reactions to intradermally placed antigens, are able to manage infections with viruses, fungi, and mycobacteria, and have normal graft rejection.

Nezelof-DiGeorge Syndrome

Nezelof,[21] DiGeorge,[12] and others described patients with another form of congenital immunologic deficiency: normal serum immunoglobulins but a lack of cell-mediated immunity, severe lymphopenia, thymic hypoplasia or absence, and death following persistent infection with mycobacteria, viruses, or fungi.

Swiss Type Agammaglobulinemia

Swiss authors, including Glanzmann,[14] Hitzig,[16] and others, collected a group of infants who appeared normal the first few weeks of life but then developed infections which disseminated and invariably led to death. Several of these patients were identified when they developed severe progressive disease following immunization with BCG or smallpox vaccine. Laboratory studies revealed both deficient immunoglobulin levels and defective cell-mediated immune responses.

THE TWO-COMPONENT IMMUNE SYSTEM

Further studies based on patients with congenital abnormalities of the immune system were similar to those cited, and were accompanied by many experiments in animals, in which the effect of manipulation of the immune system could be determined. Extirpation of the bursa of Fabricius, a collection of lymphoid tissue in the terminal gut of birds, resulted in a clinical syndrome that resembled Bruton's agammaglobulinemia, whereas neonatal thymectomy in rodents, chicks, or rabbits produced animals with the equivalent of the "Swiss type" of agammaglobulinemia.

All these studies together provided the basis for our current concept of the two component immune system. Normally cells in the bone marrow, stem cells, differentiate into thymus-dependent small lymphocytes (T cells), the mediators of cellular immunity, or into plasma cells (B cells) which become capable of synthesizing specific antibodies. In congenital forms of immunologic deficiency, stem cells with the ability to differentiate one way or both ways are lacking.

ACQUIRED IMMUNE DEFICIENCY INFECTION

Hodgkin's Disease, Other Lymphomas and Leukemias

Patients with lymphomas such as Hodgkin's disease, leukemia and other malignant disease may acquire immunologic deficiencies secondary to their disease or its treatment and have impaired ability to resist infection. Hodgkin's disease is perhaps the best studied of these conditions. The proportion with immune deficiency varies with the stage of disease, whether or not the patient has been treated with radiotherapy or chemotherapy, and the method of testing for cell-mediated immunity.

In a group of *103 untreated* patients with Hodgkin's disease, Young et al.[29] reported 11.7 per cent with skin test anergy; none was in stage I, and only 26.6 per cent of patients with stage IV disease had no reaction to any of the 6 skin tests applied. Aisenberg,[1] in his recent review, showed similar relationships to stage of disease and type and duration of treatment, but found that 60 to 70 per cent of patients in stages II, III, and IV were anergic. Patients with other malignant diseases such as lymphosarcoma, reticulum cell sarcoma, and acute leukemia, although not as thoroughly studied, also showed involvement of the immune response and a high frequency of infections especially late in disease or following intensive treatment with cytotoxic agents.

Casazza,[9] in a review of the records of 139 patients with lymphoma who died at the National Institutes of Health, reported that 25 per cent had no infections through the course of their illness; the other 75 per cent had an average of 1.3 episodes per patient. The majority of infections were due to common bacterial agents, although viral, fungal, mycobacterial or mixed etiology accounted for 30 per cent of the infections in those with Hodgkin's disease.

The characteristic type of immune deficiency and relative kind and frequency of infection in patients with lymphomas and leukemia are summarized in Table 1.

Homograft Recipients

Similarly, patients who receive homografts and those who receive immunosuppressive drugs for nonmalignant diseases (nephropathy,

Table 1. *Characteristic Immune Deficiency and Frequency of Infection in Patients with Lymphomas and Leukemia*

	ANTIBODY SYNTHESIS	"CELL" IMMUNITY	INFLAMMATORY REACTION	INFECTION BACTERIAL	INFECTION VIRAL
Chronic lymphatic leukemia	++++[1]	+	±	+++	+
Lymphosarcoma	++			+	±
Reticulum cell sarcoma	+			+	±
Acute leukemia	+	+	++++	++++	++
Chronic myeloid leukemia	0			±	±
Hodgkin's disease	±	++++		+	++++

[1]Severity of deficiency or frequency of infection indicated by scale of + to ++++.

Crohn's disease, systemic lupus erythematosus) have an increased risk of infection which varies with the kind, dose, and duration of their immunosuppressive therapy and the kind, dose, and duration of therapy with "prophylactic antibiotics."

INFECTIONS IN THE IMMUNOSUPPRESSED PATIENT

Early Experience

In the early days of transplant surgery, death of patients with overwhelming sepsis within the first 3 months postoperatively was common. During the 3 to 40 month follow-up of 111 patients who received renal transplants at the University of Colorado[24] between November 1962 and December 1965, 55 patients died and complete autopsy data were available on 51. Systemic mycotic infections with Candida were diagnosed at autopsy in 12, Aspergillus in 5, Nocardia in 2 and Histoplasma in one. In addition, 3 patients had mixed fungal infections. The lung was the site of involvement in 19, but 11 of these patients had evidence of infection in other organs as well. In 4 cases, all caused by Candida, infection was present only in the gastrointestinal tract. Sputum cultures obtained from 14 of 19 patients with pulmonary involvement revealed the infecting fungus in 6. Antemortem diagnosis and treatment of fungal infection occurred in only 2 patients. Concomitant bacterial infection – pneumonia or sepsis usually due to pseudomonas, staphylococcus or enteric bacteria – was present in 19 of the 23 patients. *Pneumocystis carinii* was present in the lungs of 5 cases and cytomegalovirus in 13.

More Recent Experience

A marked diminution in the frequency of infection and infectious death in the immunosuppressed host since 1965 has been indicated by several studies, especially that by Anderson and collaborators,[2] again at the University of Colorado. They observed that 82 per cent of all infections sufficiently severe to be contributory to death, occurred in patients who received their kidney transplants prior to 1966. In a group of 194 renal transplant recipients treated from 1962 through 1968, all followed for a minimum of 18 months or until removal of the transplanted kidney or death, 20 per cent had no infectious complications, 35 per cent had an infection that caused or contributed to death, and the remaining 45 per cent had only nonfatal infections. Factors associated with infection leading to death were severe renal failure (and the accompanying use of high dose immunosuppressive therapy), high dose prednisone therapy, and the accompanying hyperglycemia and leukopenia. The majority of patients died with bacterial infections although some succumbed to disease caused by viral, fungal, or pneumocystis agents.

The Colorado experience was similar to that reported by Briggs[5] and others in Boston and Simmons[26] and collaborators from Minneapolis. The incidence of infection in allograft recipients was related to the amount of immunosuppression and most infections were bacterial in etiology. Among 8 episodes of life-threatening pneumonia reported by Briggs, 6

were due to bacteria, and in 2 cases, both interstitial in type, no definite etiology could be established. The authors were of the opinion that the infrequent use of antibiotics in their patients prior to the development of pneumonia was responsible for the high incidence of common pathogens. Each patient in this series was gravely ill; nevertheless, all but one recovered fully.

MANAGEMENT OF INFECTION

Common Infections

The development of fever in immunosuppressed patients requires prompt attention: Chest x-ray examination and appropriate cultures should be taken immediately. Antibiotics effective against the "most likely" etiologic agents should be started early; delay in therapy may markedly affect the prognosis. Temporary cessation of immune suppressive therapy and reduction of prednisone dose to minimum levels sufficient to handle the stress of infection may aid the patient in overcoming infection. Modifications in the therapeutic regimen must be made depending on further etiologic information, course, or change in x-rays. Infection is a grave threat to the immune-deficient patient, but prompt aggressive, rational management may be life saving.

Less Common Infections

In the less frequent situations in which infection in the immune-suppressed individual is not due to a common bacterial agent and treatment with a rational combination of antibiotics is ineffective, the etiologic possibilities are innumerable, the diagnostic procedures are complex, and in many cases the forms of treatment are hazardous and of questionable effectiveness. Furthermore the signs and symptoms of various infectious syndromes may be most unusual and not lead one to the proper diagnosis.

A partial list of less common agents associated with infection in the immunologically compromised host includes *Coccidioides immitis*, giardia, atypical mycobacteria, poliovirus, *Listeria monocytogenes*, strongyloides, schistosomes, and so on. Some of the more frequently seen uncommon causes of infection will be discussed (see Table 2).

Toxoplasmosis

Toxoplasma infection in the immune-suppressed patient with or without neoplasia is characterized typically by prolonged fever, peripheral lymphadenopathy, hepatosplenomegaly and less frequently enlargement of hilar or mediastinal nodes. However, central nervous system involvement[8] with seizures, coma, obtundation, and hemiparesis is not uncommon. Diagnosis may be made by serologic studies or isolation of the organism by inoculation of mice. Toxoplasmosis in adults may be successfully treated with sulfadiazine, 4 gm. per day, and pyrimethamine, 25 mg. per day.

Table 2. *Some Less Common Causes of Infection in the Immune-Deficient Patient*

INFECTION	SYMPTOMS	DIAGNOSIS	TREATMENT
Toxoplasmosis	Prolonged fever; lymphadenopathy (hilar, peripheral); CNS: encephalitis	Isolation; serology (Sabin dye test or complement fixation test)	Sulfadiazine Pyrimethamine
Pneumocystis carinii	Interstitial pneumonia	Stain of sputum, bronchial brush, lung aspirate, lung biopsy	Pentamidine isethionate or sulfa and pyrimethamine
Aspergillosis	Pulmonary: Necrotizing bronchopneumonia, infarction; (intracavitary fungus ball rare); Pulmonary and disseminated: Intestinal, CNS, renal, thrombosis, infarction, hemorrhage	Cultures often negative; mixed infection frequent	Amphotericin B
Candida	Mucocutaneous, disseminated; may be associated with other infections	Culture – smear	Amphotericin B
Herpes simplex	Mucocutaneous, GI, Pulmonary, CNS, Disseminated; not usually fatal	Isolation; antibody rise (neutralization test)	Idoxuridine; cytosine arabinoside
Herpes zoster – varicella	Local skin lesions; frequently disseminated; pulmonary, CNS	Appearance and distribution of rash; culture, serology (complement fixation test)	Zoster immune globulin (ZIG) prophylactically; idoxuridine
Cytomegalovirus	Inapparent infection; "CMV Mononucleosis:" fever, leukopenia, lymphocytosis; hepatitis; intestinal pneumonia	Antibody rise (complement fixation test); isolation; histology	Idoxuridine; cytosine arabinoside

Pneumocystis

The prompt diagnosis and treatment of *Pneumocystis carinii* pneumonia in the patient with a "compromised" immune system generally leads to marked clinical improvement;[13] however, it is difficult to determine which patients with diffuse interstitial pneumonitis are infected with the pneumocystis organism. Examination of properly stained specimens of sputum for cysts are rarely positive. Percutaneous lung aspiration or preferably open lung biopsy appear to be the most reliable techniques for making a diagnosis, although bronchial washings may be positive in some cases. No serologic method is currently available. Treatment with pentamidine isethionate should be continued for a full 14 days unless precluded by an elevation of the blood urea nitrogen or hypoglycemia. Treatment with sulfadiazine, 4 gm. per day, and pyrimethamine, 25 mg. per day, is an acceptable therapeutic alternative. Patients with pneumocystis infection frequently have concomitant infections with bacteria, viruses, or fungi, and treatment with multiple agents may be required.

Aspergillosis

Aspergillosis should be considered in the immunosuppressed host with progressive pulmonary infiltrates who does not respond to antibacterial therapy. Diagnosis is difficult to make and treatment is seldom effective. Among 93 patients with aspergillosis reported from the Memorial Sloan-Kettering Cancer Center,[17] 59 had antemortem fungal cultures and only 7 were positive. Amphotericin B was administered to 14 patients either because of a presumptive or culture-proved diagnosis. All these patients had malignant disease and the long-term survival was most closely related to the course of the primary disease rather than to treatment of the aspergillus infection. One patient with an aspergillus "fungus-ball" was treated by surgical excision with a good response.

VIRUS INFECTIONS

Viral infection, particularly with herpes simplex virus, cytomegalovirus, and varicella-zoster, all members of the herpesvirus family, is relatively frequent in immunosuppressed patients. The course of a virus illness in such patients may be protracted or complicated by superinfection with bacterial or fungal agents, but is seldom fatal. Chemotherapy of viral infections is not of proved effectiveness and in many cases where treatment may have been indicated, the diagnosis is not made until late in the disease or at postmortem examination. The characteristics of infection with the more frequently occurring viral agents will be reviewed. Hopefully, early diagnosis and proper management will increase further the proportion of immunosuppressed patients surviving these infections.

Herpes Simplex

Recurrences of herpes labialis were no more frequent following renal transplantation than before, among a group of 55 Danish patients[28] who

survived at least one month following surgery. In none of the first 60 patients who died following transplantation in Denver, was herpesvirus recovered at autopsy (cytomegalovirus was found in 30, Herpes zoster in 1).

In an attempt to determine the significance of Herpes simplex infection in one group of immunosuppressed subjects – those with hematologic malignancy – Muller[18] and collaborators reviewed the records of patients seen at the Mayo Clinic from 1960 through 1969. There were 20 patients with various hematologic malignancies and herpesvirus infection. No deaths were attributable to the herpetic infection. In 16 cases the lesions remained localized, in 3 there were crops of lesions involving several sites and in one patient there was a generalized varicelliform eruption from which herpesvirus was isolated.

Nash[20] found histologic evidence of herpetic infection in the esophagus and/or middle and lower respiratory tract in a large proportion of burned patients and cited reports in the literature describing similar findings in the immunosuppressed host. He suggested that the frequency of herpes simplex infection may be underestimated because of inadequate diagnostic procedures.

An uncommon but severe form of herpes infection involves the central nervous system. Price et al.[22] described a patient with Hodgkin's disease and impaired immunity in whom signs of a progressive encephalitis developed over a 7 week period, terminating in death. Clinical and laboratory findings were so atypical that even with 2 brain biopsies diagnosis was delayed until approximately 6 weeks after onset when it was made by the indirect hemagglutination method. This case illustrated the fact that in the immunosuppressed individual, herpesvirus may produce a bizarre, diffuse encephalitis quite unlike that seen in the individual with a normal immune system.

Thus, herpes simplex infection in the immunosuppressed patient may be underdiagnosed because of the unusual clinical manifestations produced – esophageal, respiratory tract, or central nervous system involvement rather than the more familiar and less serious mucocutaneous form.

Varicella-Zoster

Varicella and herpes zoster represent different clinical manifestations of infection with the same agent. Varicella, a generalized disease, is seen in the young, susceptible host as the initial infection following which varicella-zoster virus may remain in a dormant form in dorsal root ganglia. Activation of this virus may be provoked by waning immunity, trauma, irradiation, or suppression of the immune system secondary to malignant disease, chemotherapy, or factors unknown. Virus replicated in cells of the dorsal root passes retrograde via sensory nerves to skin endings where the typical dermatome distribution of rash occurs. Normally the rash remains localized, but in some hosts, especially those with deficient immune systems, generalized, occasionally fatal disease may occur.

It is the impression of many physicians that herpes zoster occurs

with greater frequency among immunosuppressed populations but published reports do not support such a contention. The incidence of varicella-zoster disease among renal transplant patients, those with Hodgkin's or other hematologic neoplasms and normal persons over the age of 50 years is 8.2, 8.0, 7.9, and 9.1 per cent respectively.[23] The immunosuppressed patient, however, is more likely to have the generalized form of zoster and lesions apparently take longer to evolve and to heal. Despite this increased morbidity, serious complications are relatively uncommon and the varicella-zoster virus is not often implicated as the principal cause of death.

Cytomegalovirus

Active cytomegalovirus infection can be established by virus isolation or serologic methods in over 50 per cent of renal transplant recipients and in a large proportion of patients with malignant disease. Most individuals in whom cytomegalovirus infection exists have no related symptoms, as is the case with the normal host. A syndrome resembling mononucleosis with fever, adenopathy, and atypical lymphocytes, but absence of heterophile antibody, has been reported by many investigators. The course is generally 1 to 3 weeks in duration and uncomplicated.

Craighead[10] recovered cytomegalovirus from the lungs of 12 of 16 renal allograft recipients. In 8 patients the infection was associated with histologically demonstrable inclusion-bearing pulmonary cells, but with frank pneumonia in only 2. It is difficult to determine the significance of the cytomegalovirus infection in 6 of these patients, the histologic changes were meager, and there had been no clinical evidence of pulmonary dysfunction.

Cytomegalovirus infection is apparently common in the immunosuppressed host. Some patients develop a mononucleosis syndrome 6 to 12 weeks post transplant. The occasional patient has pneumonia but most patients are asymptomatic.

Measles, Vaccinia, and Other

Other viral infections occasionally produce severe or even fatal disease in the immunosuppressed host. Measles may result in an atypical giant cell virus pneumonia which can occur in the absence of the typical measles rash. Smallpox vaccination of the immunologically incompetent host may progress to vaccinia gangrenosa, generalized vaccinia and death. It is worthwhile to emphasize that the immune incompetent patient should receive *no live* vaccines: no smallpox, measles, rubella, or Sabin polio immunization.

Any debilitated patient, including the immunosuppressed, may be vulnerable to pneumonia and a severe illness with influenza virus infections. Attempts should be made to protect susceptible patients from exposure, if possible, and to immunize them with polyvalent influenza vaccine. (This is a *killed* virus vaccine.) Even if the immune response is not normal, there may be some protection produced.

SUMMARY

The frequency of infection in the immunosuppressed patient—especially the transplant recipient—is decreasing but there is also a concurrent shift from a predominantly "common bacteria" etiology to a wide range of unusual agents and unusual clinical manifestations. In patients with malignant disease, infections are most likely to occur in the late stages when there is diffuse involvement by neoplastic cells and widespread toxicity from therapeutic agents. In the allograft recipient infection appears to be related to rejection phenomena and intensive immunosuppressive therapy. Minimal interference with the immune mechanisms of the host and the prompt initiation of appropriate diagnostic and therapeutic measures are the most effective ways to affect mortality from infection.

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