

**Memorandum**

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From Medical Officer, Surveillance Unit
Task Force on Kaposi's Sarcoma and Opportunistic Infections

Subject Surveillance of Diseases Associated with Unexplained Acquired Cellular
Immunity Deficiency: Case Definitions and Patient Classification

To Task Force Core Staff

Unexplained acquired cellular immunity deficiency (UACID) appears to be responsible for the current epidemic of Kaposi's sarcoma and opportunistic infections. This memorandum explains the case definitions and patient classifications we are using for surveillance of UACID. Comments on how these might be improved are welcome.

Our surveillance of UACID has 3 basic objectives:

- (1) to monitor the incidence trend;
- (2) to generate hypotheses of associations between UACID and various diseases;
and,
- (3) to provide sampling frames for epidemiologic studies of UACID.

These objectives cannot be met with a single case definition of UACID. Ideally, cases of UACID would be ascertained by immunologic tests. The tests that are sufficiently sensitive and specific for the UACID of the current epidemic, however, are too expensive to apply to routine incidence trend monitoring. But they can be used on relatively small samples of patients with particular diseases to suggest previously unrecognized associations between those diseases and UACID.

TREND MONITORING

Since it is impractical to use immunologic tests to ascertain cases of UACID for routine monitoring of the incidence trend, we do not monitor UACID directly. Instead, we monitor the incidence trend of diseases associated with cellular immunity deficiency (CID). The incidence of diseases having a weak association with CID may vary greatly independently of the incidence of CID. To avoid incorrect impressions about the incidence of UACID, we must, therefore, monitor the incidence of only those diseases that are highly predictive of CID. For this purpose, we have selected diseases that are known to occur, in the majority of cases, among hosts with CID (recognized by their having lymphoproliferative malignancies or iatrogenic immunosuppression due to cancer therapy or prevention of organ transplant rejection).

For the incidence of diseases highly predictive of CID to reflect the incidence of UACID, cases with known causes of CID should be excluded. Otherwise, variation in the incidence of known causes of CID may create a false impression of variation in the incidence of UACID. For trend monitoring, therefore, we exclude from

consideration as cases of diseases predictive of UACID those patients whose diseases began during another underlying disease or physiologic condition known to cause or be associated with CID, or after an exposure to a chemical or physical agent known to cause CID.¹ These exclusion criteria are listed in Table 1.

Of the patients remaining after excluding those with any of the criteria in Table 1, we include as cases those who have had any of the following illnesses:

1. Kaposi's sarcoma, involving any part of the body, diagnosed by autopsy or biopsy;
2. Pneumocystis carinii pneumonia, diagnosed by autopsy, biopsy, or cytology;
3. Toxoplasmosis of the central nervous system or disseminated, diagnosed by autopsy or biopsy;
4. Cryptosporidiosis of the intestine causing symptoms (diarrhea) for more than 1 month, or disseminated cryptosporidiosis, diagnosed by autopsy, biopsy or "string test;"
5. Herpes simplex virus infection of any internal organ, or with mucocutaneous involvement of at least 5 weeks duration, continued spread and no healing, or with mucocutaneous involvement of at least 61 cm (2 feet) diameter, diagnosed by autopsy, biopsy, cytology, or culture of the involved sites;
6. Varicella zoster virus infection of any internal organ, or with extensive mucocutaneous involvement of 3 or more dermatomes, diagnosed by autopsy, biopsy, cytology, culture, or clinical appearance;
7. Cytomegalovirus infection with symptomatic involvement of any internal organ except the liver, diagnosed by autopsy, biopsy, cytology, or culture of the symptomatically involved sites;
8. Cryptococcosis, meningitis or disseminated, diagnosed by autopsy, biopsy, cytology (e. g., India ink preparation), or culture of involved sites;
9. Invasive candidiasis of esophagus, stomach, or intestine, or with dissemination to parenchymatous internal organs, diagnosed by autopsy or biopsy, providing that the patient has not had severe burns or cardiac or gastro-intestinal surgery within 1 month before onset;
10. Invasive aspergillosis of esophagus, stomach, or intestine or with dissemination to parenchymatous internal organs, except that pulmonary involvement should be included only if the patient has no chronic lung disease (e.g., asthma, emphysema, chronic bronchitis, histoplasmosis, sarcoidosis, tuberculosis, or atypical mycobacteriosis), and diagnosed by autopsy, biopsy, or potassium hydroxide preparation from involved sites;
11. Mucormycosis of any internal organ, diagnosed by autopsy, biopsy, or culture of involved sites;
12. Nocardiosis of any internal organ, except that pulmonary involvement should be included only if the patient has no chronic lung disease, and diagnosed by autopsy, biopsy, or culture of the involved sites;
13. Atypical mycobacteriosis (any species other than tuberculosis) of any internal organ, diagnosed by culture, except that pulmonary involvement should be included only if the patient has no other chronic lung disease;
14. Progressive multifocal leukoencephalopathy.

In the above, lymph nodes are not considered internal organs.

Patients having none of the aforementioned exclusion criteria (Table 1), and one or more of the illnesses described above, are classified "A-1." The "A" denotes absence of exclusion criteria, and the "1" denotes presence of one of the selected diseases predictive of CID. Only A-1 patients are counted in our routine determination of the incidence of diseases associated with UACID, and in routine univariate and bivariate tabulations of cases.

Occasionally we encounter patients who would be classified A-1 except for having been diagnosed by a method considered less reliable than that required for A-1 cases. Such questionable cases are classified "A-2." Among such "class 2" diagnoses may be the following:

1. Pneumocystis carinii pneumonia diagnosed by respiratory symptoms, pulmonary infiltrate on chest X-ray, failure to identify other organisms causing pneumonia on examination and culture of sputum, and presence of serum antibodies to Pneumocystis;
2. Toxoplasmosis, disseminated or with central nervous system involvement, diagnosed by neurologic abnormalities, abnormal CAT scan of the brain, presence of serum antibodies to Toxoplasma, and no evidence of alternative neurologic diagnoses;
3. Invasive candidiasis of the esophagus, diagnosed by symptoms of difficult or painful swallowing, abnormal "barium swallow" X-ray of the esophagus, and presence of oral candidiasis, or endoscopic visualization of characteristic white plaques which, when viewed microscopically in a potassium hydroxide preparation, reveal hyphae (although candida may be present, invasion has not been demonstrated).

Patients with questionable (class 2) diagnoses of one illness may yet be classified A-1, if, in addition, they have a definite (class 1) diagnosis of another illness. Non-routine tabulations that include both A-1 and A-2 cases will be specified as such.

GENERATION OF HYPOTHESES OF THE SPECTRUM OF DISEASES ASCRIBABLE TO UACID

Previously unrecognized associations between UACID and particular diseases may be suggested by surveillance data. This may occur in 3 ways:

- (1) Occurrence of rare diseases among patients classified as A-1 on the basis of other diseases already known to be predictive of CID;
- (2) Occurrence of rare diseases among patients with immunologic test results demonstrating abnormalities characteristic of A-1 cases; or,
- (3) Immunologic test results with abnormalities characteristic of A-1 cases occurring among patients with rare diseases.

The immunologic tests may have been done because the patient belongs to a group at high risk for UACID (e.g., Haitians, homosexual males, or intravenous drug abusers).

Despite immunologic test results demonstrating UACID, a patient should not be classified A-1 unless he or she has a disease selected for incidence trend monitoring. Otherwise, the apparent incidence would vary with the availability of immunologic test data, which is inconsistent at best. In the absence of one of the selected diseases, the diagnostic class is "0," and the patient may be classified "A-0."

The presence of immunologic test evidence of UACID may be denoted by a third variable in the surveillance classification code placed to the left of the letter "A." (We have not yet added this variable to the classification code in the print-outs.) Possible values for this variable, and their meanings, are as follows:

- 1: T-helper lymphocyte concentration is below normal (under $468/\text{mm}^3$);
- 0: Lymphocyte subset concentrations, responses to mitogens, and responses to antigens to which there is serologic evidence of prior exposure are all normal;

(blank): Neither of the above.

Patients with this variable equaling "1" provide us with an idea of what may be the spectrum of different clinical manifestations of UACID. It must be remembered, however, that an association between UACID and a particular disease is only hypothetical until a comparison has been made of the incidence of that disease in cohorts with and without UACID, or of the prevalence of UACID in patients with and without the disease. Because of the usefulness this variable for generating hypotheses concerning the "spectrum" of UACID, I call it the "spectrum indicator."

SAMPLING FRAMES

For epidemiologic studies of UACID, sampling frames consisting of A-1 patients or 1-A patients (i.e., 1-A-1, 1-A-2, 1-A-0) may be used. Patients who have one of the exclusion criteria (Table 1) may also be useful for special studies. Examples of studies of patients with exclusion criteria are the following:

- (1) Follow-up of surviving patients who had only a short course of corticosteroids or who had been pregnant (categorized "F", for "follow-up" instead of "A") to discover whether diseases predictive of CID continued to occur after more than 1 month since termination of the steroids or the pregnancy. If so, they may be reclassified from F-1 to A-1;
- (2) Clinical and laboratory evaluation and follow-up of patients aged 60 or more years (categorized "E," for "elderly," instead of "A") to determine to what extent they have the same CID as occurs in the younger A-1 cases of UACID;
- (3) Monitoring the incidence trend of selected rare lymphoreticular malignancies (categorized "C," for "Cancer," instead of "A") to determine if it is increasing like that for A-1 diseases. If so, it would imply that such malignancies may be effects rather than a causes of CID.

Other patient categories are "D": patients having other malignancies (except Kaposi's sarcoma), and "B": patients with exclusion criteria other than those belonging to categories C, D, E, or F.

SEARCHING FOR CASES

Our search for cases is aimed at A-1 patients. Data on patients with other than class 1 diagnoses or with exclusion criteria are only collected incidental to the search for A-1 patients.

REFERENCES

Oleske JM, Minnefor AB. Viral and Chlamydial Infections. In: Grieco H, (ed.). Infections in the Abnormal host. Yorke Medical Books, New York, 1980:382-405.

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TABLE 1

CASE EXCLUSION CRITERIA

1. Genetic or developmental defect causing "primary" cellular immunity deficiency (CID);
2. Senescence (assumed present at age 60 or more years) at onset of disease predictive of CID;
3. Neonatality (age under 28 days at onset of disease predictive of CID);
4. Ionizing radiation (a large dose, as for radiotherapy) within 5 years before onset of disease predictive of CID;
5. Systemic immunosuppressive chemotherapy or anti-lymphocytic serum (e.g., for cancer or organ transplant) within 5 years before onset of disease predictive of CID;
6. Systemic corticosteroid therapy within 1 month before onset of disease predictive of CID;
7. Pregnancy within 1 month before onset of disease predictive of CID;
8. Invasive cancer (other than Kaposi's sarcoma), regardless of whether diagnosed before or after onset of disease predictive of CID;
9. Diabetes mellitus requiring insulin therapy, at or within 1 year after onset of disease predictive of CID;
10. Renal disease with uremia or treated by dialysis, at onset of disease predictive of CID;
11. Severe malnutrition at (having developed before) onset of disease predictive of CID;
12. Sarcoidosis, regardless of whether before or after onset of disease predictive of CID;
13. Leprosy, regardless of whether before or after onset of disease predictive of CID;
14. Collagen diseases, regardless of whether before or after onset of disease predictive of CID.