Clinical picture of primary HIV infection presenting as a glandular-fever-like illness

Hans Gaines, Madeleine von Sydow, Pehr Olov Pehrson, Per Lundbergh

Abstract
The clinical symptoms and signs were assessed in 20 consecutive patients developing infection with the human immunodeficiency virus (HIV). All were male homosexuals and all presented with a glandular-fever-like illness. Changes in laboratory values were compared with findings in 40 HIV negative male homosexual controls.

In the 10 patients for whom date of exposure to the virus could be established the incubation period was 11-28 days (median 14). One or two days after the sudden onset of fever patients developed sore throat, lymphadenopathy, rash, lethargy, coated tongue, tonsillar hypertrophy, dry cough, headache, myalgia, conjunctivitis, vomiting, night sweats, nausea, diarrhoea, and palatal enanthesa. Twelve patients had painful, shallow ulcers in the mouth or on the genitals or anus or as manifested by oesophageal symptoms; these ulcers may have been the site of entry of the virus. During the first week after the onset of symptoms mild leucopenia, thrombocytopenia, and increased numbers of banded neutrophils were detected (p<0.005). The mean duration of acute illness was 12.7 days (range 5-44). All patients remained healthy during a mean follow up period of 2-5 years.

Heightened awareness of the typical clinical picture in patients developing primary HIV infection will alert the physician at an early stage and so aid prompt diagnosis and help contain the epidemic spread of AIDS.

Introduction
In 1984 a patient was described in whom a mononucleosis-like illness was associated with seroconversion to the human immunodeficiency virus (HIV). Similar cases were later reported by Cooper et al and other workers. We now know that the primary infection with HIV may be asymptomatic or associated with either a mild flu-like illness or neurological manifestations. Our knowledge about the clinical course of primary HIV infection, however, is based on case reports and retrospective investigations.

We report a study of 20 consecutive cases of primary HIV infection presenting as a glandular-fever-like illness and describe the symptoms, signs, and results of routine laboratory investigations.

Subjects and methods
The study was performed at the departments of infectious diseases, Roslagstull Hospital, Stockholm, which serve a population of about 820000. Each year the departments treat an average of 3800 inpatients and 12600 outpatients. About 550 patients infected with HIV—that is, one third of all known HIV positive people in Sweden—were followed up at our hospital during the study period. From December 1984 to November 1986 we enrolled all patients who fulfilled the following criteria: (a) a clinical picture suggestive of primary HIV infection; lack of other obvious cause of illness; (c) a history of possible exposure to HIV before onset of illness; (d) willingness to give informed consent.

Twenty men aged 18-49 (mean 32.7) years were enrolled in the study (none refused). All were homosexual. Twelve patients were admitted to hospital for a mean of 6.3 (range 3-13) days, the others being seen once a week or more as outpatients. All patients recorded daily the presence or absence and severity of various symptoms. Great emphasis was placed on elucidating a history of possible exposure to HIV during the three months before the illness. A close doctor-patient relationship was established with one of us (HG) and repeat interviews carried out. All possible sexual contacts during the three months before the illness were offered an HIV test.

As laboratory controls we used 40 consecutive healthy HIV negative homosexual men who had consulted for HIV testing during 1985-6.

Standard methods were used for all chemical laboratory measurements. Methods of laboratory confirmation of primary HIV infection and the results have been reported. All patients were tested for IgG and IgM antibody activity against cytomegalovirus (enzyme linked immunosorbent assay; ELISA) and Epstein-Barr virus-viral capsid antibody (immuno-fluorescence). In addition, serological tests with acute and convalescent samples were performed for rubella, morbilli, herpes simplex, varicella zoster, influenza A and B, adenovirus, enterovirus, respiratory syncytial virus, and mycoplasma (complement fixation or ELISA); hepatitis A and B (radioimmunoassay); heterophile antibodies (rapid slide tests); and syphilis (Wassermann reaction). In varying numbers of cases we tried to culture virus from faeces (enterovirus), nasopharynx (influenza, parainfluenza, adenovirus, respiratory syncytial virus, urine (cytomegalovirus), mouth ulcers, genital ulcers, and anal ulcers (herpes simplex)); bacteria from blood, nasopharynx, throat, faeces, urine, and mouth and genital ulcers; and candida from mouth and genital ulcers.

Electrocardiograms and chest radiographs were obtained when indicated in about half the patients and abdominal and oesophageal x ray pictures in three.
abnormally distributed samples—that is, those that were neither arithmetically nor logarithmically normally distributed.

Results

INCUBATION PERIOD

All 20 patients had a history of definite or probable exposure to HIV during the three months before the onset of symptoms. Ten men had had sexual intercourse only once with a new partner during that period; all six partners available for examination were HIV positive. The incubation periods in the 10 men were 11, 13, 14, 14, 14, 14, 14, 15, 27, and 28 days.

In three patients the incubation period could not be determined accurately, each had had sexual intercourse with a new partner on several occasions. The

ranges of probable incubation periods in these men were 7-31, 7-56, and 8-49 days, respectively. Two of the three partners were tested and found to be HIV positive. The incubation periods could not be assessed in the remaining seven patients, as over a long period each had had several sexual partners or sexual intercourse on many occasions with one partner. All five available partners of these seven patients were HIV positive.

On the occasions of probable transmission of infection 12 of the 20 men had been engaged in both receptive and insertive activity (three anogenital, two orogenital, seven anogenital and orogenital), six in receptive activity only (four anogenital, two orogenital), and two in insertive activity only (anogenital). None had used condoms. Besides these sexual contacts the patients denied possible exposure to HIV during the three months before illness.

SYMPTOMS AND SIGNS

All 20 patients had an acute onset of illness with malaise and chills followed by other symptoms and signs over the next one or two days (table I).

General—Myalgia in the back, arms, or legs occurred in four cases and general aching in four. Weight loss of 5-9 kg within two to six weeks occurred in four patients.

Mouth, throat, and respiratory tract—Nineteen patients complained of a sore throat. On examination we noted a coated tongue and inflammation of the pharynx and soft palate, in six cases associated with enanthema of the hard palate—that is, deep red circular patches some 5 mm diameter, often distributed asymmetrically. In a further six patients, the soft palate and oval shallow ulcers 5-10 mm diameter with white bases and ringed by a thin red zone were seen. All six patients had severe pain on swallowing. None of the six gave a past history of aphthous stomatitis. The ulcers, which appeared during the first days of illness and disappeared over the ensuing week, were distributed on the inner surfaces of the lips and floor of the mouth in two patients, whereas the tonsils, soft palate, and uvula (rare sites for aphthous ulcers) were affected in four. Tonsillar hypertrophy appeared towards the end of the first week in nine of the 16 patients who still had their tonsils. Non-productive cough, more troublesome than other symptoms, was reported by nine patients.

Lymph nodes—Generalised lymphadenopathy appeared at the end of the first week. The enlarged nodes were usually soft and not tender. Those along

---

**Note:** The above text is a summary of a medical document discussing the incubation period and symptoms of HIV infection. For a more detailed and accurate understanding, please refer to the full document. The text is not a comprehensive medical report and does not capture all the details and nuances present in the original document. The tables and figures are not included in this summary.
Laboratory values in relation to onset of symptoms. Points represent individual patients. ○ = Patient with grossly abnormal erythrocyte sedimentation rate. □ = Patient with grossly abnormal serum enzyme activities. Dotted lines indicate normal values. Solid lines and shaded areas represent mean and 1 SD calculated by polynomial regression of running average (see text).

sternocleidomastoid were the most prominent. Patients had a mean of 10 enlarged nodes (range 0-25), about one third of which were estimated to have a maximal diameter of ≥1 cm.

Skin—Fifteen patients had a rash. In all cases it affected upper trunk and neck; in nine face and forehead or arms, or both; and in three scalp, lower trunk, and tops of thighs. The rash consisted of 10 to several hundred slightly raised, pink to deep red, non-confluent maculopapules 5-10 mm diameter, with fairly well demarcated borders. The presence and character of the rash were not influenced by antibiotics. Four patients with rash also had a solitary, painful lesion 5-10 mm diameter, which was oval-round, shallow, and had slightly raised borders. These lesions were found on the penis in two cases and on the skin-mucosa border of the anus in two. The lesions appeared on days 1 to 3 after the onset of illness and disappeared spontaneously in about a week.

Gastrointestinal tract—Severe retrosternal pain on swallowing occurred in five patients, three of whom suffered massive weight loss due to dehydration. In a fourth patient the weight loss was associated with massive watery diarrhoea and vomiting.

Neurological—One man suffered bladder paresis and asymmetric severe back pain, which appeared on the 15th day of illness and disappeared eight days later. Primary herpes simplex type II infection was excluded, as antibodies to this agent were detected in a frozen serum sample obtained two years earlier. Cerebrospinal fluid could not be examined, as he refused a lumbar puncture. The symptoms were possibly due to polynuropathy or neural root disorder.

LABORATORY FINDINGS

The figure gives the results of routine laboratory investigations during the illness, and Table II analyses these statistically in relation to control values. During the first week of illness circulating platelet and white cell counts were low (p<0.0005) and the proportion of banded neutrophils increased (p<0.0001). During the third and fourth weeks of illness there was increase in the proportion of circulating lymphocytes and a decrease in neutrophils (p<0.0005). Atypical lymphocytes were detected in fewer than half the patients. Grossly abnormal results in two cases distorted the mean plots for sedimentation rate and liver function values shown in the figure.

C reactive protein concentrations were normal in seven patients and slightly raised in five. Examination
of cerebrospinal fluid for cells and protein in two patients with high fever and headache persisting for more than a week gave normal results. Additional laboratory measurements, including serum alkaline phosphatase activity, showed nothing abnormal.

IgG antibody to HIV appeared from the second week of illness in all 20 patients. IgM anti-HIV was detected in all 19 patients adequately sampled during the first three months of illness. HIV antigen in all 13 tested in the first three weeks of illness, and HIV cultured from plasma in all six patients tested during the first two weeks of illness.

Candida was isolated in two out of four specimens obtained from mouth ulcers, whereas both specimens obtained from genital ulcers were free of candida. Attempts to culture herpes simplex virus (six patients) or bacteria (four patients) from ulcers yielded negative results. Herpes simplex virus was isolated in material from an anal ulcer in one man who had a history of recurrent anal herpes simplex. All other cultures and serological evaluations for viral and bacterial pathogens gave negative results, including the rapid slide tests for heterophile antibodies.

The patient with grossly abnormal liver function values (figure), which returned to normal over the next one to two months, had serological evidence of past infection with Epstein-Barr virus, cytomegalovirus, and hepatitis B but not hepatitis A. In his case testing for IgG and IgM antibodies to cytomegalovirus in three sequential serum samples and two attempts to isolate cytomegalovirus from urine showed no evidence of active infection with this agent.

All electrocardiograms and chest, abdominal, and oesophageal radiographs were normal.

DURATIONS OF ACUTE ILLNESS AND CONVALESCENT PHASE

The duration of the acute illness (mean 12.7 days; range 5-44) was 5-7 days in nine patients, 8-14 in seven, and over 14 days in four patients. The end of the acute illness was marked by general improvement and, in most cases, return of the temperature to normal. In 12 cases there followed a convalescent phase associated with severe lethargy in 10 patients (prolonged night time sleep and sleeping during the day), general malaise in nine, low grade fever in four, and, less frequently, myalgia, nocturnal sweating, and sore throat. Most patients were fully recovered clinically by four weeks after the acute illness, though four had symptoms persisting for two to nine months. Two patients developed seborrhoeic eczema in the convalescent period. The virus persisted but all patients remained healthy during a mean follow up period of 2.5 years (range 1.5-5.3).

Discussion

We believe that the clinical and laboratory findings in this series of patients identified over two years by a "typical" clinical picture accurately represent the glandular-fever-like illness of primary HIV infection. Though the findings refer to male homosexuals in Stockholm, they are probably also valid for people infected by other routes.

Special emphasis was placed on elucidating the history of exposure to HIV as a reliable basis for estimating the incubation period. We find that it may be difficult to obtain an accurate history of exposure at the initial examination of a patient with suspected HIV infection. In several patients in this series a detailed history was not obtained until a close doctor-patient relationship had been established. Somewhat unexpectedly, 10 of the 20 men had evidently contracted HIV infection from a single sexual encounter. All the sexual contacts available for examination were HIV positive. Their serological patterns indicated longstanding HIV infection (high antibody titres reactive against several "late" HIV antigens), so excluding the possibility of their having caught the infection from our patients. The incubation period of about two weeks in most cases (range 11-28 days) agrees with 23 other reported cases.1 9-25 Incubation periods of six to eight weeks have been reported in four patients.1 9-25 An incubation period assumed to be six days was reported for one man who had not had sexual intercourse during the two to six weeks before the onset of illness because of recurrent anal herpes simplex. His incubation period, however, may have been more than six weeks.

A particularly interesting finding in our study was the high incidence of ulcers, localised to different sites. Ulcers were seen in seven of the 20 patients and suspected in a further five. In the two patients with genital ulcers bacteriological, virological, and mycological cultures of samples yielded negative results, but findings of syphilis serology were negative on follow up. Chancroid, granuloma inguinale, and lymphogranuloma venereum were not excluded, but spontaneously healing ulcers in the presence of normal local lymph nodes are not typical of these diseases, which moreover are extremely rare in Sweden. We recovered candida from two of the four specimens obtained from mouth ulcers, but this organism may be isolated from the throats of most healthy people. Furthermore, antibiotics had been given to both patients, which may predispose to growth of candida. Thus there was no evidence of a causal relation between candidal infection and the ulcers. The five patients with retrosternal pain on swallowing were not subjected to endoscopy. Their symptoms, however, were characteristic of ulcers, with severe pain at a certain stage of swallowing, in three cases more or less precluding taking oral fluids.

Though aphthous ulcers have been reported, genital ulcers have been described in only one patient, who had shallow ulcers of the penis and scrotum.2 to Our knowledge anal ulcers have not been noted before and oesophageal ulcers have been reported in only one case.4 Dysphagia, however, is common and may indicate oesophageal ulcers. Two patients with oral ulcers also had genital ulcers or retrosternal pain, whereas in 10 cases ulcers were exclusively localised to mouth, penis, anus, or (possibly) oesophagus. In each case the ulcers were localised to a site involved in the sexual activity practised on the occasion of probable transmission of infection. The cause of these ulcers is unknown, but in view of our findings it seems possible that the human immuno-deficiency virus may be implicated and so be a "chance" of primary HIV infection. In other studies anti-HIV seropositivity has been found to correlate with a previous history of genital ulceration.4 5 The interpretation has been that pre-existing lesions, due to other infections or trauma, may be more likely than intact skin or mucosa to allow HIV to enter. Though this may be true, in our series genital and extragenital ulcers appeared not before but at the onset of illness—that is, around two weeks after the probable date of infection.

With exception of the ulcers, our findings in respect of symptoms, signs, duration of illness, and the convalescent phase accord with those reported in single cases. Neurological symptoms occurred in only one patient, which agrees with the results of others.19 Bladder incontinence was described but several case reports have shown that a great variety of neurological manifestations may be associated with primary HIV infection—for example, encephalitis, meningitis, myelitis, and neuritis.2 6 28 We consider some of our laboratory findings to be of diagnostic importance, though they are not specific for primary HIV infection—for example, the mild leucopenia and thrombo-
cytopenia as well as the increased proportion of circulating banded neutrophils detected during the first week and increased proportion of lymphocytes compared with neutrophils during the third to fourth weeks. For differential diagnosis of primary HIV infection versus Epstein-Barr virus and cytomegalovirus infections normal laboratory findings may have additive diagnostic value; atypical lymphocytosis or abnormal liver function values were rare in our patients.

Our study comprised cases of primary HIV infection identified by a "typical" glandular-fever-like illness.1 We emphasise, however, that patients with primary HIV infection may have an "abortive" or influenza-like illness. Patients with such mild disease may not consult a doctor, and if they do the diagnosis may be missed as only general, uncharacteristic symptoms such as fever, night sweats, malaise, fatigue, and myalgia may be noted. In other cases the primary infection may be subclinical, with the possible exception of lymphadenopathy.1, 10 Neurological manifestations of primary HIV infection have been reported without other symptoms1, 4 but more commonly complicate an abortive1, 2, 4 or typical illness.1, 2, 4, 9

All our patients were homosexual men, though the study was designed to enrol all patients with typical primary HIV infection presenting with a mononucleosis-like illness irrespective of mode of infection. Possibly there is a low rate of transmission in other populations. Seropidemiological studies in the Stockholm area, however, found a rapidly increasing rate of seropositivity among intravenous drug addicts during 1985-6, the number acquiring HIV infection during that period reportedly being equal to that of homosexual men. Possibly also intravenous drug addicts may be less likely to seek medical attention than are homosexuals. Careful history taking of the 300 or so HIV infected intravenous drug addicts being followed up in our outpatient department failed to disclose any case of typical illness at the time of seroconversion. To our knowledge no case of mononucleosis-like illness caused by HIV among drug addicts has been reported.

By contrast, occasional patients infected with HIV by accidental needlestick or heterosexual contact have had a typical illness at the time of seroconversion.1, 4, 9 As in haemophiliacs, transplant recipients, and transfusion recipients, abortive1, 2, 20 atypical,11, 12 and neurological13, 14 forms of primary HIV infection have been reported except in five cases in which a rash was observed in an otherwise non-typical illness.1, 11, 12, 13 In these five cases, however, the aetiology of the rash was not established or an atypical (compared with our patients) rash appeared after the acute illness. Thus cases of typical illness have been reported in patients infected sexually or by accidental needlestick but not among those sharing injection equipment or receiving blood, blood products, or organ transplants with transmission of HIV directly into the blood stream. Reasons for the differences in manifestations of primary HIV infection are unknown but may be related to differences in the primary target cells, which may be related to the portal of entry of the virus or to differences in immunological states among infected people.

All our patients presented with a mononucleosis-like illness. Many conditions may cause a mononucleosis-like syndrome and serological investigations are required for the aetiological diagnosis. Nevertheless, most of the alternative causes may be excluded clinically, as illustrated by comparing our findings with those in infectious mononucleosis associated with Epstein-Barr virus,11, 16-18. The onset of illness in infectious mononucleosis is usually insidious, rarely with symptoms other than malaise and low grade fever during the first four days. By contrast, the onset of primary HIV infection is sudden, with the development of full blown illness during the first one or two days. Both conditions may give rise to abnormalities in the mouth and throat, but these differ considerably. Tonsillar hypertrophy is often very prominent in infectious mononucleosis but mild in HIV infection; the enanthema of infectious mononucleosis is confirmed to the border of the soft and hard palates but affects the hard palate in primary HIV infection; and exudative pharyngitis is seen in 50-60% of patients with infectious mononucleosis but so far has not been recorded in primary HIV infection, whereas the occurrence of ulcers seems specific for primary HIV infection. In addition, infectious mononucleosis seems to be more uniform and occurs more often in primary HIV infection than in infectious mononucleosis (provided that antibiotics have not been given).

Most patients with infectious mononucleosis have an enlarged liver and spleen, whereas patients with primary HIV infection do not. Watery diarrhoea and coughing, which are frequent and often severe in primary HIV infection, have been considered to have a negative diagnostic value in infectious mononucleosis. Relative lymphocytosis of >50% and atypical lymphocytosis of >10% occur in 80-90% of patients with infectious mononucleosis but in only a few patients with HIV infection. In infectious mononucleosis 90% of patients have raised serum transaminase and alkaline phosphatase activities and 8% of patients are jaundiced. In our primary HIV infected patients, activities were only infrequently raised, and serum bilirubin concentrations and alkaline phosphatase activity were normal in all patients examined.

In summary a glandular-fever-like illness may be seen in primary HIV infection. This clinical picture of HIV mononucleosis may be distinguished from other causes of the mononucleosis syndrome on the basis of clinical findings. Nevertheless, a possible diagnosis of HIV infection must always be confirmed serologically and it should be remembered that ELISA for HIV antibodies may yield negative results at the time of the acute illness.15 Tests which may help with the diagnosis in this early phase of HIV infection include methods for detecting HIV antigen16 or IgM antibodies.17

We thank Professor Öran Strannegård and Associate Professor Marianne Forgren for their help and constructive criticism, Professor Gunnar Eklund for valuable statistical advice, and Pharmacia Diagnostics AB for help with computer analysis.

11 Valle SL, Febrile pharyngitis as the primary sign of HIV infection in a cluster of cases. Lancet 1986;i:826-7.
14 Ranki A, Valle SL, Krohn M, et al. Long latency precedes overt seroconvert-
Pursuing efficacy in surgical practice

John H Wyllie, Iain G Kidson, David H Wyllie

Abstract

To examine fluctuations in numbers of patients on surgical wards the dates of admission and discharge of each of the 5556 patients admitted from 1 January 1985 to 31 December 1987 were examined during computerised audit of a single surgical firm. The numbers of patients under the care of the firm fluctuated widely, often exceeding the 38 beds nominally available. Duration of stay varied from two days or less (3062 admissions) to more than a month (163 admissions). One patient was in hospital for 278 days. The patients admitted for more than a month (2-9% of the total) filled 28% of the beds; not all these patients were elderly.

A further increase in throughput of patients undergoing elective operations might be achieved by always admitting patients on the day of operation, and perhaps by discharging patients even sooner than at present. Efficiency would increase but so would overall costs.

Introduction

An efficient surgical service should have a high throughput of patients and a low rate of cancellation. It is difficult to run: during a lull the beds and lists seem wastefully underused, and during a spate of emergencies elective operations have to be cancelled. These fluctuations have received scant attention. In 1984 we set up a computer system for audit on our general surgical firm, which has special interests in vascular and oesophageal surgery. We looked at records for 1985, 1986, and 1987 to see how the load on the wards fluctuated and to find where economies might be made to preserve the service should financial stringency demand a cut in the number of beds.

Data collection

For all inpatients and for patients having operations on an outpatient or day case basis house surgeons recorded the following details on a microcomputer: the hospital number; surname; sex; age; consultant in charge; whether admission was emergency or elective; date of admission or transfer; date of discharge, transfer, or death; and up to four diagnoses, complications, and operations. These data were checked at the weekly meeting of the whole firm (two consultants, a senior registrar, a registrar, and three house surgeons) at which we review our work; diagnoses were modified as necessary each week until the patient was discharged. Programs to analyse the data were written.

This paper deals with patient episodes; any patient appears as many times as he or she was admitted during the study. Duration of stay was calculated as zero days if the patient was discharged on the date of admission, one day if discharge was on the day after admission, and so on. As this does not allow estimation of the number of beds required for day cases we assumed that for a stay of zero days the requirement was 0·5 bed/day.

Results and discussion

NUMBERS OF ADMISSIONS AND BEDS USED

From 1 January 1985 to 31 December 1987 there were 5556 admissions. Table I shows that the number of emergencies rose by 18·8% and of elective opera-

1368