A Syndrome Resembling Infectious Mononucleosis After Open-heart Surgery

D. R. SMITH,* M.D., M.R.C.P.

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The use of an extracorporeal circulation in open-heart surgery is now standard practice, and deaths directly attributable to perfusion are unusual. Nevertheless, a significant morbidity may be associated with such procedures, and in recent years more attention has been directed to the causes of such morbidity.

Kreel *et al.* (1960) were the first to comment on the presence of atypical lymphocytes in the peripheral blood of patients two to three weeks after perfusion. A clinical post-perfusion syndrome of fever and splenomegaly with atypical lymphocytes in the peripheral blood was described by Seaman and Starr (1962). This syndrome has been further amplified by the reports of Perillie and Glenn (1962), Wheeler *et al.* (1962), Holswade *et al.* (1963), and Anderson and Larsson (1963). So far 33 examples of the syndrome have been described.

The present paper presents a further nine examples and compares the findings in these patients with those previously described.

Material.—Between 1 January 1961 and 31 July 1963 173 open-heart operations were carried out at Hammersmith Hospital using cardiopulmonary bypass. Nine examples of the syndrome were encountered in this period.

Incidence.—The incidence of the syndrome in this series was 5.2%. This figure is higher than that of just over 3% recorded by Perillie and Glenn (1962) and Seaman and Starr (1962) but lower than the 11% reported by Wheeler *et al.* (1962). In common with previous authors, no particular age or sex incidence was noted in the present series. A tendency for the syndrome to occur in sporadic outbreaks was noted. This point is discussed more fully below.

Clinical Features

The clinical features of the nine patients are summarized in the Table.

Fever occurred as the presenting symptom in seven patients. The onset of fever varied between the 21st and 34th post-operative days (mean 27 days), typically arising about two to three weeks after the normal post-operative fever had subsided. The elevation of temperature was prolonged, the duration varying between 10 and 21 days (mean 17 days). Marked variations in severity were seen, however, one patient having frequent rises of temperature to 104° F. (40° C.) in contrast to another in whom the reading was never higher than 99.5° F. (37.5° C.). General well-being was apparent despite the presence of fever. Two patients remained afebrile, although showing otherwise typical manifestations of the syndrome.

Fever appears as the commonest presenting symptom in the cases previously described, occurring in 16 out of the 19 fully documented patients. In those reported by Wheeler *et al.* (1962) and Perillie and Glenn (1962) the time of onset of the fever was similar to that of the present series, being first noted on the 19th to the 37th post-operative day. Seaman and Starr (1962) record the development of fever on the ninth post-operative day, but full clinical details of this patient are not given in their report. Presentation as early as this seems unusual. Previous reports confirm that the fever is usually of prolonged duration and that a minority of patients may remain afebrile throughout the illness.

Splenomegaly was detected in all patients in the present series and in 30 of the 33 previously described cases. In our patients it was noted 48 hours after the onset of fever in three instances, and in the remainder after an interval varying from 7 to 21 days. In the two patients who remained afebrile throughout, the finding of splenomegaly on the 26th and 55th post-operative days respectively led to the diagnosis of the syndrome. The noting of splenomegaly in an asymptomatic patient also indicated the presence of the syndrome in two instances in the series of Wheeler *et al.* (1962).

Previous reports show wide variation in the timing of the appearance of splenomegaly, it being noted 1 to 17 days after the onset of fever. All authors are in agreement that, when present, splenomegaly persists many months after other features of the syndrome have disappeared.

The degree of splenomegaly is never great. In the present series the largest spleen was palpable 6 cm. below the costal margin.

Hepatomegaly was noted in only one patient, but was present in 13 of the 23 earlier cases where reference is made to this point. The onset appears closely to parallel the appearance of splenomegaly, but it has been of short duration only. Marked enlargement has not been reported.

Lymphadenopathy was noted in seven of the nine patients, appearing concurrently with the splenomegaly and varying in duration from 4 to 14 days. There was a discrete, shotty enlargement of the anterior and posterior cervical and, occasionally, the axillary groups. Marked enlargement of lymph nodes did not occur. Similar lymphadenopathy was noted by Perillie and Glenn (1962) in their three cases, but was not commented upon by Wheeler *et al.* (1962) or Seaman and Starr (1962). Holswade *et al.* (1963) noted lymphadenopathy in only one of their 14 patients, but the frequency of its occurrence in the present series suggests that it may be a fairly common manifestation of the syndrome.

A transient, non-pruritic maculopapular rash was seen in four patients, it being noted in each instance concurrently with the appearance of splenomegaly. In one patient the rash faded after 24 hours, but in the others it persisted for three to five days. In two patients the trunk alone was affected; in the remainder the rash was generalized. Although the lesions were never profuse, in general they most resembled those of rubella. The occurrence of such a rash in the syndrome has not been previously described.

Laboratory Data

Peripheral Blood

The finding of *atypical lymphocytes* in peripheral blood films is regarded as essential for the diagnosis of the syndrome. In the present series atypical lymphocytes were present on the day

* From the Department of Medicine, Postgraduate Medical School and Hammersmith Hospital, London.

of onset of the syndrome in eight of the nine cases. The remaining patient developed fever on the 23rd post-operative day, but atypical lymphocytes were not found until the 38th post-operative day. Instances of similar delay in the appearance of the atypical lymphocytes are quoted by Perillie and Glenn (1962) and Seaman and Starr (1962).

The *total white-cell count* was raised above 10,000/c.mm. in only two patients, the highest figure being 14,000/c.mm. The tendency for total white-cell counts to be most frequently normal or low is noted by all previous authors, although a leucocytosis may occasionally occur.

The *percentage of atypical lymphocytes* present varied considerably, the highest figure being 35% of the total white-cell count, while only occasional atypical cells were seen in one patient. This variability in the numbers of atypical lymphocytes present is in keeping with previously reported experience. The atypical lymphocytes found in the syndrome are indistinguishable from those occurring in infectious mononucleosis, and are variously termed virocytes, glandular-fever cells, or Downey cells (Downey and McKinlay, 1923).

Eosinophilia amounting to 5–10% of the total white-cell count was noted by Perillie and Glenn (1962) in their three patients. Other authors have not confirmed eosinophilia as a feature of the syndrome, and it was absent in the present series.

Paul-Bunnell tests were carried out in all patients after the appearance of atypical lymphocytes in the peripheral blood. Unfortunately, serial tests were performed in only four patients (see Table). Negative results were obtained in seven patients. One patient (Case 4) had a positive result from a test taken shortly after the appearance of splenomegaly and atypical lymphocytes on the 55th post-operative day, the titre after guinea-pig absorption being 1:160. Of particular interest is the remaining patient (Case 1), who had a negative result three days after the onset of fever, but positive findings when the test was repeated on the 12th day of fever (titre after guinea-pig absorption 1:160). A positive result from the Paul-Bunnell test appears to be unusual in the syndrome, only one example being found in the 33 previously reported cases (Holswade *et al.*, 1963).

Toxoplasma complement-fixation and dye tests were carried out in three instances in the present series with negative results.

Illustrative Case Reports

The commonest presentation of the syndrome is at the occurrence of fever in the third or fourth post-operative week.

Case 1 represents the most dramatic form of the illness yet encountered, and is unusual in that the Paul-Bunnell test was positive.

Case 1

A schoolgirl aged 16 underwent pulmonary valvotomy and closure of a patent foramen ovale on 13 March 1962. Hypothermia and cardiopulmonary bypass with a Melrose-N.E.P. machine were used. Blood for the operation was taken into "edgludate" anticoagulant on the day before operation and heparinized before use in the machine. These techniques were employed for all patients in the present series.

After operation a persistent ejection systolic murmur was audible, the jugular venous pressure was raised 10 cm., and the liver was palpable 2 cm. below the costal margin. These signs were attributed to residual right ventricular outflow obstruction. Digoxin and chlorothiazide were started and a good diuresis followed with the loss of 4 kg. in weight. The liver became impalpable although the jugular venous pressure remained 6 cm. above the sternal angle. Symptomatically she was well and afebrile until the 27th post-operative day, when there was an abrupt onset of a fever, rising to 104° F. (40° C.) with rigor. The only new finding on examination was slight faucial hyperaemia. The haemoglobin was 13.8 g./100 ml.; W.B.C. 6,000/c.mm. (50% neutrophils, 40% lymphocytes, 1% eosinophils, 1% monocytes, 8% atypical lymphocytes). The rigor proved to be the beginning of 20 days' remittent fever with the temperature ranging between 100 and 103° F. (37.8 to 39.4° C.). By the third day of fever the faucial hyperaemia had subsided, but tender, slightly enlarged anterior and posterior cervical lymph nodes were palpable. The largest node was estimated to be 1 cm. in diameter.

On the 14th day of fever a generalized maculopapular rash appeared and faded slowly, finally disappearing on the 19th day of fever. On this day, however, the spleen became palpable 2 cm. below the costal margin. Several blood counts were performed during the illness, all showing considerable numbers of atypical lymphocytes. Although the total white-cell count was never raised, atypical lymphocytes constituted up to 18% of the count. The Paul-Bunnell test was negative on the third day of fever but positive on the 12th day (titre 1:320, and after guinea-pig absorption 1:160). Blood cultures were sterile throughout and no antibiotics were given. By the 47th post-operative day the fever showed no signs of settling and prednisolone 40 mg./day orally was begun. This was followed by resolution of the fever within 48 hours.

After seven days, during which time she had remained afebrile, the dosage of steroids was progressively reduced, and this treatment was finally discontinued after a total of 17 days' therapy. The spleen slowly decreased in size and only the tip was palpable on discharge 38 days after the onset of the illness. Subsequent follow-up has been quite satisfactory. No sequelae are apparent and a good result has been achieved by the operation.

Case 7

This is an example of the more frequently encountered milder manifestations of illness.

A schoolboy aged 7 had a ventricular septal defect closed by direct suture on 26 March 1963 under whole-body perfusion and hypothermia. Post-operatively no cardiac murmurs were audible

Summary of Cases

Case No.	Age and Sex	Diagnosis	Date of Operation	Fever: Onset Post-op. Day	Fever: Duration (Days)	Splenomegaly: Post-op. Day Noted	Splenomegaly: Duration	Lymphadenopathy: Post-op Day Noted	Lymphadenopathy: Duration (Days)	Rash: Post-op. Day Noted	Rash: Duration (Days)	Atypical Lymphs: Post-op. Day Noted	Atypical Lymphs: Max. %	Eosinophils: Max. %	W.B.C. Max. Total per c.mm.	Paul-Bunnell: Post-op. Day	Paul-Bunnell: Result	Paul-Bunnell: Titre
1	16 F	V. P.S.	13/3/62	27	20	46	About 3 weeks	30	4	41	5	27	18	1	7,000	30 39	Neg. Pos.	1: 160
2	16 F	I.S.	12/4/61	34	17	41	?	41	10	None		34	35	1	6,000	43 48	Neg. „	
3	7 F	O. Secun. A.S.D. + V.P.S.	11/7/61	28	10	35	?	None		35	3	35	Occasional	1	6,000	37	„	
4	9 F	O. Primum A.S.D.	21/4/61	None		55	?	55	14	None		55	13	3	3,600	57	Pos.	1: 160
5	11 F	V.S.D.	5/6/62	23	16	23	?	23	10	23	1	38	11	5	14,000	25 38	Neg. „	
6	15 M	V.S.D.	19/7/62	32	21	32	About 4 mths	None		None		34	18	2	8,000	34 70	„ „	
7	7 M	V.S.D.	26/3/63	21	18	23	?	23	7	None		24	16	4	13,000	29	„	
8	19 M	V.A.S.	13/3/63	24	15	45	?	40	4	38	3	34	Many	1	7,000	42	„	
9	6 F	V.P.S.	3/4/63	None		26	?	26	?	None		26	14	2	9,000	26	„	

V.P.S. = Valvular pulmonary stenosis. V.A.S. = Valvular aortic stenosis. A.S.D. = Atrial septal defect. V.S.D. = Ventricular septal defect. I.S. = Infundibular stenosis. *Hepatomegaly* was noted in only one patient (Case 7), appearing on the 31st post-operative day and persisting for three days. *Toxoplasma complement-fixation and dye tests* were carried out in Cases 7, 8, and 9 with negative results. *Negative Paul-Bunnell tests*—titre after guinea-pig absorption less than 1: 5.

and general progress in the early post-operative period was excellent. Fever up to 101° F. (38.3° C.) persisted for the first four post-operative days, but settled by lysis. Normal temperatures were recorded one week after the operation. On the 21st post-operative day the patient was fully convalescent and his discharge was contemplated, but fever recurred. A low-grade fever persisted for the next 18 days, the highest temperature recorded being 100.4° F. (38° C.). At the time of onset of fever no abnormality could be found on physical examination to account for its presence. Two days later, however (the 23rd post-operative day), discrete, non-tender enlargement of the anterior and posterior cervical groups of lymph nodes was noted, and the tip of the spleen could just be felt. The splenomegaly subsequently increased, the spleen being palpable 6 cm. below the costal margin on the 27th post-operative day. It thereafter slowly regressed. The lymphadenopathy persisted unchanged for a week before rapidly resolving. The largest gland noted was only 1 cm. in diameter. At no time were axillary or inguinal nodes affected. Slight non-tender hepatomegaly was found on the 31st post-operative day, the liver being palpable 3 cm. below the costal margin. It rapidly returned to normal over the next three days. No rash was seen at any time.

On the third day of fever (the 24th post-operative day) the white-cell count was 8,000/c.mm., 31% neutrophils, 58% lymphocytes, and 11% atypical lymphocytes, the latter cells resembling those appearing in glandular fever. By the 39th post-operative day the white-cell count had risen to 13,000/c.mm., atypical lymphocytes comprising 16% (neutrophils 24%, eosinophils 4%, basophils 1%, lymphocytes 55%). Paul-Bunnell and toxoplasma complement-fixation and dye tests, taken on the 29th post-operative day, were both negative.

The illness ran a benign course and the patient was discharged three days after the fever had subsided—that is six weeks after the operation.

General malaise was strikingly absent during the latter part of his stay in hospital. At the time of discharge the tip of the spleen could still be felt and 11% atypical lymphocytes persisted in the peripheral blood. When seen again one month later he was well, the spleen was not palpable, and the white-cell count had returned to normal.

Discussion

Fever, splenomegaly, and the presence of atypical lymphocytes in the peripheral blood constitute the characteristic triad of the syndrome, the onset of which occurs most frequently in the third or fourth week after operation. Hepatomegaly, lymphadenopathy, and a rubelliform rash may be present, but are less common features. In all reported cases the illness has been benign and self-limiting, its particular importance lying in the fact that it often develops at a time when the patient is fully convalescent from operation and ready for discharge from hospital. Awareness of the existence of the syndrome may preclude prolonged investigation and unwarranted treatment for subacute bacterial endocarditis.

The aetiology of the syndrome remains uncertain. Perillie and Glenn (1962) stressed the presence of eosinophilia and suggested that an immune reaction might be a factor in the pathogenesis. Eosinophilia was, however, absent in the present series. A variety of drugs are often given during the post-operative care of a patient after open-heart surgery, but no single drug has been incriminated as a possible cause of the illness. In previously reported cases the only constant factor appears to have been the use of cardiopulmonary bypass. The type of oxygenator used (rotating disk or bubble) has differed, but a common denominator has been the use of large volumes of donor blood, both in the actual surgical procedure and in the initial priming of the pump. Holswade *et al.* (1963) favoured a viral aetiology because of the presence of atypical lymphocytes in the peripheral blood. It seems reasonable to suggest that viral disease may be transmitted to a susceptible recipient via donor blood, for the transmission of homologous serum jaundice is well known to occur in this manner. The fact that instances of the syndrome have not been reported after the use of blood transfusion in other surgical procedures does not necessarily argue against this hypothesis. Larger volumes of blood tend to be used in open-heart surgery than in other procedures, and a situation akin to the occurrence of homologous serum jaundice from the use of pooled plasma may arise.

Further support for the theory of an infectious aetiology is given by a tendency, shown in the present series, for cases to occur in sporadic outbreaks. Although the study spanned a period of three years, from 1961 to 1963, and three cases were seen in each year, all examples of the illness occurred between March and July. This is unlikely to be coincidental, as surgery continued throughout the year. A tendency towards sporadic outbreaks of the syndrome was also noted by Holswade *et al.* (1963). Of 14 cases they report, spanning four years, eight occurred in one year.

The relative constancy of the time interval between operation and the development of symptoms is in keeping with either an infectious or an immune aetiology.

The clinical similarities between this syndrome and that of infectious mononucleosis are immediately apparent, and it is tempting to suggest that a relationship exists. Although Pfeiffer (1889) described the clinical entity of glandular fever, doubt still exists regarding both its diagnosis and its nature. Although the infection is generally assumed to be due to a virus, attempts to isolate viruses have failed (Bang, 1943; Evans, 1960). Leibowitz (1953) thought that a positive Paul–Bunnell test "can be utilized as an almost absolute yardstick for the diagnosis of infectious mononucleosis." One patient in the present series (Case 1) fulfilled this criterion, a positive Paul-Bunnell test being found on the 12th day of illness, the test having previously been negative. This patient must therefore be regarded as having infectious mononucleosis. The test was positive in a further patient (Case 4) on the second day of illness, but serial tests were not done, and thus it is possible that the patient contracted infectious mononucleosis some months or weeks before operation. Although there was nothing to suggest this possibility in the history, it is known that subclinical varieties of infectious mononucleosis occur with some frequency and that the Paul-Bunnell titre may remain elevated for a long time after such an attack (Hobson *et al.*, 1958).

Some experimental data are available to support the suggestion that a clinical illness fulfilling Leibowitz's criteria for the diagnosis of infectious mononucleosis can be transmitted by donor blood.

Wising (1942) and de Vos and Kuipers (1951) each report one example of the transmission of "seropositive" infectious mononucleosis by blood transfusion, their work being carried out in an attempt to confirm the viral nature of the disease by deliberate transmission of illness to volunteers. A single virus may not necessarily be the cause of the clinical entity of infectious mononucleosis. Both Shubert *et al.* (1954) and Hobson *et al.* (1958) favour, on clinical and epidemiological grounds, the view that "seropositive" and "seronegative" infectious mononucleosis are different diseases. In the study of Hobson *et al.* (1958) 242 cases were Paul-Bunnell-positive and 100 Paul-Bunnell-negative, although the clinical features of each group were typical of the illness usually diagnosed as infectious mononucleosis. Whether single or multiple viruses are responsible for the clinical syndrome of infectious mononucleosis, the infrequency of positive Paul-Bunnell tests in the post-perfusion syndrome therefore remains compatible with the view that the illness is closely related to infectious mononucleosis. Although potential blood donors are screened before giving blood, it is possible that infection may be transmitted from an asymptomatic donor, as little is known about the duration of infectivity of infectious mononucleosis.

Summary

Nine further examples of a post-perfusion syndrome resembling infectious mononucleosis are described. The major features of the syndrome—namely, fever, splenomegaly, and

the presence of atypical lymphocytes in the peripheral blood—have already been described and the findings of previous authors are reviewed. Attention is drawn to the presence of lymphadenopathy, which appears to occur more often than suggested by earlier reports. A transient rubelliform rash was noted in four of the nine patients—a previously unrecorded manifestation of the illness.

Awareness of the syndrome may prevent unwarranted investigation or treatment for subacute bacterial endocarditis.

Although the aetiology is uncertain, it is suggested that it is most reasonable to regard the syndrome as a viral disease closely related to infectious mononucleosis and that it is transmitted by blood transfusion.

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Myocardial Infarction-like Syndrome in Cholecystectomized Patients Given Narcotics

SANFORD M. MOSSBERG,* M.D.

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Morphine, codeine, and pethidine (meperidine, *U.S.P.*) are known to produce contraction of the sphincter of Oddi, elevation of intrabiliary pressure, and pain in the chest or abdomen (Gaensler, McGowan, and Henderson, 1948 ; Curreri and Gale, 1950). Although hyperamylasaemia can follow narcotic administration in normal individuals (Bogoch, Roth, and Bockus, 1954), a narcotic-induced rise of serum glutamic oxaloacetic transaminase (S.G.O.T.) activity occurs chiefly in patients with cholecystectomy or non-functioning gall-bladder (Mossberg, Bloom, Berkowitz, and Ross, 1962) Electrocardiographic changes, too, can result from increased intrabiliary pressure (Clarke, 1945).

This report describes the cases of three patients in whom the combination of chest pain, electrocardiographic abnormalities, and an elevated transaminase level was responsible for the erroneous initial impression of myocardial infarction. Recurrent elevations of transaminase activity following narcotics, a history of cholecystectomy, and absence of progression of a typical infarct pattern on the electrocardiogram all led to the recognition that myocardial infarction was being simulated by biliary-tract factors.

Case 1

A 68-year-old white housewife was admitted to Montefiore Hospital on 26 May 1958 complaining of substernal and left-upper-quadrant-pressure pains occurring intermittently for three weeks. The pains were unrelated to meals or exercise, would last from one to three hours, and could not be relieved by nitroglycerin.

Past medical history included tuberculosis and typhoid fever during childhood, acute rheumatic fever in 1933, cholecystectomy for cholelithiasis in 1950, probable myocardial infarction and gastric ulcer in 1954, duodenal ulcer in 1955, and mild congestive heart failure since 1956. Digoxin and chlorothiazide had given moderately good control of cardiac symptoms and signs, although during the week prior to admission she had noted increased exertional dyspnoea.

* From the Department of Gastroenterology, Division of Medicine, Montefiore Hospital, New York, New York, U.S.A.

Because of continuous substernal pain, pethidine, 50 mg., was administered intramuscularly six hours before admission.

Physical examination revealed a thin white woman who appeared alert and younger than her stated age. Blood-pressure was 140/74, pulse 68/min., respirations 16/min., and temperature 101° F. (38.3° C.). There was no neck-vein distension. The antero-posterior diameter of the chest cage was increased but no adventitious sounds were heard. The cardiac apex impulse was in the sixth intercostal space between the midclavicular and anterior axillary lines. A grade 2 harsh apical systolic murmur radiated to the left axilla and lower left sternal border. No diastolic murmur was heard. The second heart sound was booming over the aortic area and split over the pulmonic area. A gallop was not present. The abdomen was soft with no organ enlargement, and there was slight tenderness in the left upper quadrant. A cholecystectomy scar was present. Moderate pitting oedema extended from the ankles to the mid-leg.

Blood examination on admission showed: haematocrit 34%, white blood count and differential normal, sedimentation rate 29 mm./hour (Wintrobe), blood sugar 75 mg./100 ml., blood urea nitrogen 15 mg./100 ml., normal electrolytes, and S.G.O.T. 176 units (upper normal limit 38 units). Venous pressure was 60 cm. citrate and circulation time (dehydrocholate) 15 seconds. The electrocardiogram (Fig. 1) revealed changes which were interpreted as representing a possible myocardial infarct of the posterior wall of indeterminate age. The patient was placed on a coronary regimen, but no anticoagulants were given. On 28 May alkaline phosphatase, cephalin flocculation, and thymol turbidity were normal. On 29 May, because of shortness of breath, oxygen by nasal catheter and morphine sulphate, 8 mg., were given at 2 p.m. Blood taken at 7 a.m. the next day showed an S.G.O.T. activity of 976 units (checked for accuracy). No clinical change had taken place and the patient continued to progress satisfactorily. On 1 June pethidine, 75 mg., was given parenterally during an episode of epigastric distress, and on the following day the S.G.O.T. activity was 90 units. The possibility of extension of an infarct was considered. Upon review of the chart, however, it became apparent that no significant change had occurred in the electrocardiogram and that transaminase elevations were probably related to narcotic administration. The patient was progressively ambulated. On 23 June an episode of chest and abdominal pain was treated with barbiturates rather than with narcotics. No further S.G.O.T. rise