PREGNANCY ASSOCIATED WITH
HAEMORRHAGIC SMALLPOX

BY

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In a country where smallpox is common, one would expect an association of smallpox with pregnancy to be a common occurrence. But a careful study of the available literature shows that not many such cases have been reported.

When smallpox affects a pregnant woman, it tends to become very malignant. The sudden onset of signs and symptoms and the short duration of the disease and the rapid termination make the diagnosis extremely difficult.

The interesting clinical features and unusual and unique pathological findings together with the difficulties we had in the diagnosis make it justifiable to publish such a case.

CASE REPORT

B., a Hindu aged 25 years and gravida-2 (hospital number 59220), was admitted to the Christian Medical College Hospital, Vellore, South India, on May 2nd, 1958, at 3 p.m., with the following complaints:
Amenorrhoea, 8 months.
Fever, 2 days.
Backache and labour pains since 7 a.m. that day.

Previous Obstetrical History. Her first pregnancy was a normal delivery at term 2 years ago. The child was alive and well.

Previous Medical and Surgical History. Nil relevant.


Management. She was given penicillin injections, Codopyrine, and chloral and bromide mixture. She continued to have backache and had a restless night in spite of sedatives.

The following day it was noticed that her face was swollen and there was intense congestion of the face and the neck. Remembering that it was the season for smallpox we asked her whether she had been in contact with anybody suffering from smallpox or whether there were smallpox cases in her locality. She denied both.

Thinking that it might be due to idiosyncrasy to a drug, we suspended all the drugs. Temperature that day was 100° F.

On May 4th, 1958, at 7 a.m., purpuric haemorrhages were noted on her face, chest and extremities. To begin with these haemorrhages were very small and pin-point in size but later on became bigger, till some were as large as 1 to 2·5 cm. in diameter just before her death.

Samples of blood were taken for various tests. It was now noticed that the patient bled from every veni-puncture. There were sub-conjunctival haemorrhages also. Our tests included
estimation of fibrinogen. Blood transfusion was started and vitamin K was given. The haemorrhagic tendency increased. She had haematuria and bleeding from the gums. Thinking that it might be a rare case of hyperheparinaemia, protamine zinc sulphate and Toluidine Blue were given. She had had by now 2 pints of blood and 1 pint of gelatin. The condition progressed, haemorrhages under the skin and bleeding from the gums increased. There was no bleeding from the vagina. We noticed a few blebs about 3 to 4 in number on her extremities and these contained blood. She became restless and cyanosed, developed mental symptoms, became delirious and comatose and expired at 10.20 a.m., that is, 3 hours after the first appearance of petechial haemorrhages. The patient died undelivered.

Our diagnosis at that time was death from haemorrhage due to a blood disorder with a bleeding tendency.

The blood reports had not yet been received. A post-mortem was done and only then was the diagnosis of smallpox possible.

INVESTIGATIONS

4th May, 1958. Blood: White blood cells 67,400 per c.mm. Neutrophils, 50 per cent; eosinophils, 1 per cent; lymphocytes, 47 per cent; monocytes, 2 per cent.

Platelet count, 130,000 per c.mm. Prothrombin time, 1 minute 10 seconds (control 12.5 seconds—partial clot). Bleeding time, 3 minutes 20 seconds. Clotting time, 7 minutes 35 seconds.

Blood picture: moderate anisocytosis, moderate hypochromia and poikilocytosis, slight polychromasia, nucleated red cells, plus. Fibrinogen, normal.

Blood—Haemoglobin, 8.75 g. per cent on admission and 8.00 g. per cent at the first appearance of the petechial rash.

POST-MORTEM EXAMINATION

The body was that of a pregnant female weighing 52.5 kilograms and 5 feet 1 inch in height. A well marked coppery red flushing of the face, the neck, anterior surface of the chest and the lateral surface of the upper arms was a striking feature. Haemorrhages in the skin varying in size from a pin point to about 1 cm. in diameter were scattered over the arms, the anterior surface of the chest and abdomen, thighs and dorsum of feet (Fig. 1). Most of these purpuric spots appeared to be in the deeper layers of the skin but close examination showed a few of the lesions to be slightly raised above the surface of the skin. Such lesions were found on the thighs and gluteal regions and strongly suggested early vesicle formation. On the left palm, at the roots of the little and ring fingers circular raised blebs containing blood, about 1.5 cm. in diameter, were seen. Similar blebs were also noticed at the tips of several toes, the largest of them measuring about 2.5 cm. in diameter. Some of these blebs were broken.

On the mucosa of the palate and inner surface of the lower lip, many irregular slate grey patches ranging in size from 0.2 cm. to 0.5 cm. in diameter, were present. Marks of primary smallpox vaccination were present on the lateral surface of the right upper arm (Fig. 2).

Small haemorrhages were seen scattered on the visceral and parietal pleura, on the surface of the heart and on the endocardium, on the diaphragm, parietal peritoneum and over the entire mesentery. On the surface of the kidneys and on the mucosa of the bladder there were pin-point haemorrhagic spots. On the oesophageal mucosa there were slate coloured irregular patches of haemorrhage similar to those described in the palate. The serous and mucous coats of the stomach and the whole of the small intestine showed large patches of haemorrhage. The stomach and small intestine were filled with blood. The whole of the jejunum and the proximal one-third of the ileum showed a remarkable finding. The mucosa at this region was studded with innumerable clear vesicles 2 to 5 mm. in diameter (Fig. 3). These vesicles resembled very closely those seen on the skin in classical smallpox. These burst on pressure. The intervening mucosa showed patches of haemorrhage. The rest of the ileum showed innumerable irregular patches of haemorrhage. The caecum and colon showed no haemorrhage and did not show any vesicles.

The lungs were boggy, heavy and exuded

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**Fig. 1**

Skin over the elbow region showing purpuric rashes.

**Fig. 2**

Prominent successful primary vaccination marks on the upper arm.
FIG. 3
Numerous vesicles on the mucosa of the small intestine.

FIG. 4
Stratified squamous epithelium of palate showing typical reticular degeneration. H. & E. ×140.

D.P., I.S.
**FIG. 5**

Intracytoplasmic inclusion bodies (Guarnieri bodies). H. & E. ×1,400.
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frothy fluid from cut surfaces. The liver was slightly enlarged, weighing 1,690 g. It was pale brown with slightly rounded edges and its cut surfaces showed several brownish white circular areas varying from 1 mm. to 7 mm. in diameter.

The spleen was very much enlarged, soft and congested and weighed 255 g.

The foetus weighed 1,800 g. It did not show any haemorrhage on the skin or other obvious lesions externally. Permission for autopsy examination of the foetus was not given.

HISTOLOGICAL FINDINGS

The stratified squamous epithelium of the skin, buccal mucosa and oesophagus showed the typical features of haemorrhagic smallpox. The epithelial cells were swollen, vacuolated and showed different degrees of degeneration; outlines of the swollen degenerated cells formed a reticulum containing in its meshes a haemorrhagic exudate (Fig. 4). In several places the supporting mesh work had ruptured forming larger spaces containing exudate. These spaces were breaking through the superficial layers of the epithelium to give an appearance of early vesicle formation. In the cytoplasm of these swollen epithelial cells were seen typical Guarnieri bodies determining the specificity of these lesions. These were round or oval, eosin staining structures varying widely in size from 1 to 8 microns in diameter (Fig. 5). Several cells contained two and three of these bodies. The epithelium also showed infiltration by a number of small round mononuclear cells.

The lungs showed well marked oedema. The alveolar walls were thickened and in several areas the alveoli contained lymphocytes and large macrophages.

The liver showed a moderately severe degree of fatty change, cloudy swelling of the liver cells and several small areas of necrosis. Many Guarnieri bodies were found in the parenchymatous cells. The portal tracts showed lymphocytic infiltration.

Sections from the jejunum and ileum showed fully formed vesicles in the mucosa. The epithelial cells were swollen and varying degrees of degeneration had set in. Most of the cells were completely necrosed.

DISCUSSION

The autopsy findings, gross and microscopic, undoubtedly establish this case to be one of haemorrhagic smallpox. Two types of haemorrhagic smallpox have been recognized: (1) Variola haemorrhagica pustulosa, where the lesions mature to the vesicular or pustular stage and the haemorrhage occurs in and around these lesions; (2) a graver and a uniformly fatal form is the purpura variolosa where the disease manifests itself as a widespread purpuric rash and the patient dies before the typical rash of smallpox develops. The case presented here belongs to the latter group.

Some German authors believe that this type occurs almost exclusively in vaccinated people. Others do not agree with this. This patient had marks of successful primary vaccination. Another case of purpura variolosa, a man on whom we did a post-mortem examination, did not have any marks of vaccination. What is, however, very striking in this case is the presence of vesicles in the intestinal tract similar to those found on the skin in an ordinary case of smallpox. It is commonly postulated that in any severe form of smallpox the lesions may be manifested in a more intense degree in the gastrointestinal tract. However, authentic case reports of intestinal lesions in smallpox are few and we have been unable to find any report of a case with vesical formation. Councilman, Magarath and Brinckerhoff, as quoted by Rivers in 1948, from their wide experience with smallpox, state that the typical lesions are sharply limited to the stratified epithelium of the skin and of the mucous membranes of the soft palate, the pharynx and the oesophagus. Wolman (1951) reporting one case of purpura variolosa, mentions congestion and haemorrhages in the ileum and caecum but no vesicles. It is very interesting that when the lesions on the skin were just beginning to show vesicular degeneration, well formed vesicles had already formed in the gastrointestinal tract.

Microscopically, the so-called "reticulierende Degeneration" and "ballonierende Degeneration", seen in the stratified squamous epithelium of skin, buccal mucosa and oesophagus, were typical of any early lesion of smallpox. The pathognomonic cytoplasmic inclusion bodies
were seen not only in the epithelium of these areas, but also in the liver, spleen and intestines. The Guarnieri bodies ranged from 1 to 8 microns in diameter. First mentioned by Weighert in 1874, Guarnieri described these in detail in 1892, and believing them to be protozoan parasites, named them Cytorcytes variolae. The modern belief is that these are altered host-material containing numerous elementary bodies which are the causative virus of variola. Paschen (1906) described these structures and they are often named after him. These elementary bodies have a diameter of about 200 m. microns and are just visible under the microscope but in stained tissue sections their outlines are not discernible in the cytoplasmic inclusions.

Small foci of necrosis in liver, spleen and bone marrow are common accompaniments of haemorrhagic smallpox as in any other severely toxic disease.

The haemorrhagic tendency may be due to two factors. The numerous small necrotic areas in the bone marrow may suppress bone marrow activity and reduce platelet formation. The second and more important factor is the action of the powerful toxins on the capillary endothelium causing rupture of small capillaries.

**BLOOD PICTURE**

In the ordinary type of smallpox there is leukopenia with a relative mononucleosis but later a leucocytosis occurs. Anaemia usually occurs. In later stages depression of the bone marrow may result in alteration in the platelets, fibrinogen and prothrombin.

According to Musser (1951) in severe cases there may be an initial high leucocytosis and this may continue with an increase in the neutrophil polymorphs throughout the entire course of the disease.

In purpuric smallpox, on the other hand, the neutrophil polymorphs decrease although the total count remains high from an increase in the lymphocytes. Illingworth and Oliver (1944) mention a case where the leucocyte count was 18,000 per c.m.m. on the second day and 38,000 per c.m.m. on the fourth day. The differential count showed a leuko-erythroblastic blood picture without significant anaemia. Platelets are diminished.

**Diagnosis**

While the diagnosis of smallpox is not difficult in the majority of cases, the haemorrhagic type can be confused with such conditions as purpura and leukaemia and diagnosis may be extremely difficult. Bleeding from the mucous surfaces soon follows the cutaneous haemorrhages and in this case it occurred within 2 hours. Melaena and haemoptysis also may occur; they were absent here. Most workers stress the severe constitutional disturbances from the onset. Strangely enough in this case the constitutional disturbances were mild and the highest temperature was 100° F. In the fulminating type the patient may not survive long enough to develop the vesicular or pustular stage of the eruption. Death occurred in this case within 4 hours after the appearance of the purpuric rash. Large and irregular lesions are indicative of an extremely severe and uniformly fatal case and such cases are frequently undiagnosed. It has been suggested by some people that any case of fever with irregular purpuric lesions should be considered smallpox until proved otherwise.

Certain laboratory tests may be helpful in the diagnosis:

(1) A presumptive diagnosis could be made after microscopic examination of stained smears of a cutaneous vesicle or pustule for elementary bodies. We can expect to get the result in 1 hour. Stains should be freshly made.

(2) A final diagnosis could be made when the virus is isolated on the chorio-allantoic membrane. The growth on the chorio-allantois is found to be fairly dependable and sensitive and this test distinguishes variola from varicella virus. This test takes 3 days.

(3) The preliminary study of complement fixation tests in the diagnosis of these cases seems to yield reliable results. This test requires special hyper-immune serum.

(4) Paul's test—the contents of the pustule are applied to the scarified cornea of a rabbit. Opacities and intracellular inclusion bodies are noted in positive cases. This test requires 3 days.

**Effect of Smallpox on the Foetus**

Transplacental transmission occurs. Hence abortions, premature delivery, stillbirth and
neonatal death are common. Browne (1951) puts the stillbirth and neonatal death-rate as high as 80 per cent. The infant may be born with pock marks. It is said that the famous obstetrician Mauriceau was born with pock marks. If the mother had the disease for some time, the child may be born with healing pustules.

The children born of such mothers are said to be immune for some months and attempts at vaccination are not successful.

In this case, there were no pock marks on the foetus.

**Vaccination**

There is no contra-indication to vaccination during pregnancy, but it is not advisable to have it done in the puerperium for fear of introducing infection.

**Prognosis**

"In purpura variolosa, death is usually inevitable." Such a statement by Hunter (1956) indicates the grave nature of the disease. Similarly Sweitzer and Ikeda quote a mortality of 100 per cent in purpura variolosa. Gupta (1951) in Calcutta describes his experience with haemorrhagic smallpox in pregnancy. He treated 10 cases in all. The first 3 died before the rash appeared and diagnosis was completely missed. The rest of them had petechial haemorrhages and they all died. He also concludes that this malignant type of smallpox affected mostly pregnant women.

Herrlich (1959) in his report on an epidemic of smallpox in Bombay in 1958 mentions that the fatal course of purpura variolosa is unaffected by cortisone, acromycin or other antibiotics.

We could sum up best the present position as regards prognosis and treatment by quoting the Neapolitan paediatrician Michael Sarcone who wrote two hundred years ago: "The disease still defies all the efforts of the physician, and it is as malignant today as it was in the time of the Arabs who left us the first description of it."

**SUMMARY AND CONCLUSIONS**

(1) A case of haemorrhagic smallpox in pregnancy showing some unusual clinical features is reported.

(2) The post-mortem findings are reported and the pathological lesions are discussed.

(3) Laboratory tests may be helpful in the diagnosis of haemorrhagic smallpox.

(4) The pregnancy has an adverse effect on the disease. Haemorrhagic manifestations are common and are invariably fatal to mother and foetus.

**REFERENCES**


