The Use of Nitrogen Mustard in the Management of Two Pregnant Lymphoma Patients

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Although there have been several scattered case reports and reviews on the subject of pregnancy in lymphomatous disease,¹-⁴ there has not yet been any record pertaining to the use of nitrogen mustard in the management of the pregnant lymphoma patient. Within the last two years 2 of our patients with Hodgkin's disease became pregnant and were treated with nitrogen mustard during the course of their pregnancy.

Case Reports

Case 1, G. R.

This 26 year old white female was first seen in the Tumor Clinic at Syracuse Memorial Hospital in March 1949 with a history of cervical and axillary lymphadenopathy of ten months' duration and symptoms of fever, pruritis, anorexia and weight loss of one month's duration. Ten days prior to her admission to the Tumor Clinic an axillary node was biopsied and reported as Hodgkin's disease. Because of the generalized nature of the disease the patient was given a course of nitrogen mustard [Methyl-bis (beta-chlorethyl) amine hydrochloride] 0.6 mg./Kg. body weight which resulted in a clinical remission of one month's duration. In May 1949 because of the exacerbation of her symptoms she was given a second course of nitrogen mustard 0.6 mg./Kg. body weight. Following this she was started on x-ray therapy to her neck and mediastinum with progressive improvement. She remained well until September 1949 when pruritis returned and examination revealed an abdominal mass. X-ray therapy was directed to the abdomen with considerable improvement of her symptoms. In December 1949, following the return of peripheral adenopathy and pruritis, she was given 2.6 mg. colchicine daily for a week, followed by a two week rest period and then one more week of colchicine therapy. During that time the disease was active and progressed and no beneficial effect from the colchicine could be demonstrated.†

In January 1950 the patient was found to be four months pregnant. In view of her widespread disease it was elected to give her another course of nitrogen mustard 0.6 mg./Kg. body weight. She showed slight improvement for one month following this third course of mustard therapy. For the next three months she received only x-ray therapy to the cervical and axillary areas and supportive measures including blood transfusions. On June 29, 1950, a cesarean section was performed and a normal male infant weighing 6 lbs. 2 oz. was delivered. The placenta was normal in all respects. The patient had a postpartum course complicated by wound dehiscence. As soon as the wound closed properly she was given x-ray therapy to the chest and pelvis with some benefit. Shortly thereafter, however, she pursued a steady decline with return of active generalized disease and the development of intercostal herpes zoster. Opiates and finally bilateral pre-frontal lobotomy failed to completely relieve her pain and pruritis. She died January 23, 1951 and an autopsy revealed

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† The use of colchicine in lymphomatous disease was under investigation in our clinic at the time both of these patients were under our care. There was no apparent benefit or untoward effect in any of the patients treated with the compound.
Hodgkin's disease involving inguinal, axillary, cervical, peri-aortic, iliac, mediastinal and mesenteric lymph nodes. Hodgkin's infiltration of lung, liver, spleen, kidneys and right ovary was demonstrated.

The child was examined when 19 months of age, in our Pediatric Out Patient Department by Dr. W. Waters and has shown normal development. The routine laboratory work and bone aspiration performed in January 1952 showed no abnormalities.

Case 2, J. R.

This 26 year old white female was first seen in the Tumor Clinic at Syracuse Memorial Hospital in April 1949 with known Hodgkin’s disease of two months’ duration. Initially this patient had disease localized clinically to the cervical and axillary areas. This was effectively controlled with x-ray therapy. In December 1949 the patient was started on 2.6 mg. colchicine daily with little effect except diarrhea. She developed marked constitutional complaints for the first time in June 1950. Chest films on this occasion revealed mediastinal adenopathy. X-ray therapy was given to her mediastinum with good response.

On a routine Tumor Clinic visit in October 1950 this patient was found to be two months pregnant. She remained well until her fourth month of pregnancy in December when she again presented with axillary and mediastinal adenopathy and an acute onset of marked constitutional symptoms. At that time it was decided to give her nitrogen mustard 0.4 mg./Kg. body weight. A dramatic improvement was effected following this treatment and she had a clinical remission lasting one month. In January 1951 the patient had an acute recurrence of constitutional symptoms. Because of the generalized nature of her disease she was given a second course of nitrogen mustard 0.4 mg./Kg. body weight with only minimal improvement. Following this the patient received ACTH with only transient benefit and continued to do poorly. On March 19, 1951 in her seventh month of pregnancy this patient went into labor and a viable premature 4 lb. 11 oz. baby girl was delivered by the vaginal route using caudal anesthesia. The pathology report of the placenta revealed immature placenta with fresh infarction and intravillous fibrin deposition.

The patient remained hypotensive following the delivery and in spite of all measures lapsed into a coma and died 51 hours postpartum. An autopsy revealed Hodgkin's sarcoma involving hilar lymph nodes, abdominal peri-aortic nodes and liver, spleen, ovary and breast.

The infant had a stormy course with the development of jaundice, hepatomegaly and anemia. Three days after birth a bone marrow aspiration performed on this infant revealed decreased cellularity but was still within the limits of normal. Following whole blood transfusions the infant progressively improved. A follow-up examination on this child, at 10 months of age, was performed by Dr. W. Waters. The infant appeared to have developed normally. Routine blood examination and bone marrow aspiration were reported to be normal.

Discussion

The nitrogen mustards were first used intravenously in humans by Gilman et al. in 1942. The precise point of chemical reaction of the nitrogen mustards in vivo is not known but it is believed that one of the transformation products, probably a cyclic immonium cation, is responsible for the biological action of the nitrogen mustards. There is sufficient evidence that the basic mechanism of action of the nitrogen mustards involves a reaction with one or more important cellular enzymes. It has been observed when nitrogen mustard is given to an animal in sublethal doses a nucleotoxic action affects the rapidly growing cells such as the hematopoietic system and the intestinal mucosa. There is marked inhibition of mitosis, increased mutations and chromosome rearrangement. In sublethal doses of nitrogen mustard used clinically the cytotoxic action is
limited to the blood-forming organs. At present the clinical dosage is restricted by the occurrence of granulocytopenia, thrombocytopenia and anemia.\textsuperscript{6}

There are many reports in the literature which indicate that nitrogen mustards induce temporary remissions in generalized lymphomatous disease.\textsuperscript{5-7} Since the use of nitrogen mustard in the pregnant lymphomatous patients has no precedent clinically it would be of some interest to review briefly pertinent animal studies. Karnofsky et al.\textsuperscript{10} produced anomalies in chicks by injecting the yolk sac of three day embryos with nitrogen mustard. The surviving chicks continued to grow but at hatching showed abnormalities of the beak and legs. The experimental work of Haskin\textsuperscript{11} in 1948 and Bass et al.\textsuperscript{12} in 1950 may be more relevant to the clinical problem. Haskin, working with pregnant rats, employed nitrogen mustard and noted that if the compound was injected on the twelfth, thirteenth, fourteenth or fifteenth days of gestation gross abnormalities of development resulted. Bass et al. observed that when pregnant mice were given nitrogen mustard on the sixth or seventh day of gestation there was a definite decrease in the percentage of deliveries. However, Bass noted that in the mustard treated mice in which the young were carried satisfactorily through the normal period of gestation no abnormalities of development were found.

It is apparent that nitrogen mustard in extremely high doses injected into pregnant animals has a deleterious effect. On this basis one might speculate that possibly during a critical period of human gestation the use of nitrogen mustard might produce either serious malformations of development or even death of the fetus. It is to be noted that in the patients here reported, nitrogen mustard was administered only in the second trimester of pregnancy. Perhaps had this drug been given earlier in pregnancy, the result may have been less desirable. In our 2 patients, because of the widespread disease with severe systemic manifestations, palliation was deemed urgent. In addition, both patients were anxious that everything possible be done to enable them to go to term, regardless of any further risk to themselves. For these reasons it was decided to give these patients nitrogen mustard in spite of the possible hazards involved. We feel that both patients received sufficient salutary effect to have justified the use of nitrogen mustard. The patient G. R., who received nitrogen mustard during the fourth month of pregnancy was delivered of an infant apparently normal in all respects. The patient J. R. received two courses of nitrogen mustard during her pregnancy, 0.4 mg/Kg. body weight in the fourth and a similar course in her fifth month and it is to be noted that her infant was in poor condition at birth, but has since apparently developed normally. Whether this is evidence of toxicity of the nitrogen mustard or simply the result of prematurity and other factors cannot be established at this time. This infant, now 10 months of age, is developing normally.

**SUMMARY**

1. It is possible to use nitrogen mustard therapeutically in the management of a patient with "lymphoma" in the second trimester of pregnancy and obtain a viable infant.

2. In view of the findings noted in one of the infants, it is not possible to make a categorical statement with regard to possible deleterious effects of nitrogen mustard on the fetus.
REFERENCES

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