CLINICAL CONFERENCE

Unpredictability of Tumors in Childhood

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DR. WILLIAM RIKER: We have had a number of interesting experiences with tumors in childhood since the tumor board was started at the Children's Memorial Hospital. One of the things that has impressed us has been the unpredictability of tumors in childhood.

One of the most difficult and most unpleasant tasks we have to face as pediatricians and surgeons is to have to give a prognosis to the parents of a child who has a malignant tumor. It is very difficult to do, and it is debatable as to whether it is worse to give an excellent prognosis in the case of a favorable tumor and have the child expire from the malignancy, or to give a hopeless outlook to the parents of a child who has a usually fatal disease, only to have the child survive.

I would like to present several case histories of children in which the prognostication was very difficult.

Neuroblastoma. K.S. was a 5-weeks-old female infant when admitted to Children's Memorial Hospital May 12, 1955. Immediately prior to admission it was noticed that the abdomen was getting large and she began to regurgitate.

She was critically ill and poorly nourished. The abdomen was markedly distended with prominent veins over the upper abdomen. The liver was smooth and firm and generally enlarged; the right and left lobes extended to the brim of the pelvis. The spleen was not palpable. There was respiratory embarrassment due to the marked abdominal distention pushing up the diaphragm (Fig. 1, A).

The family history was non-contributory.

Laboratory data revealed: erythrocytes, 2,820,000/mm^3; hemoglobin, 7.7 gm/100 ml; and leukocytes, 11,250/mm^3 with normal differential. The urine was normal. The cephalin flocculation was negative; the thymol turbidity, 0.5 units; and the cholesterol, 88 mg/100 ml. The epinephrine test revealed concentrations of glucose as follows: fasting 72; at 10 min, 85; 20 min, 90; 40 min, 109; and at 60 min, 112 mg/100 ml. With the glucagon test there was a rise in concentration of glucose of 26 mg/100 ml in 60 min. Intravenous pyelograms were negative as were the heart and lungs on roentgenographic examination.

A liver biopsy was performed. Postoperatively there was wound disruption, but because of the large liver there was no evisceration.

On gross examination of the biopsy specimen there were diffusely scattered small, pin-head sized, white flaky areas. On microscopic examination the normal architecture was so altered that liver tissue could only be recognized by the small portal areas. There were diffusely scattered throughout the sections tumor cells which were stained deeply basophilic, uniform in size and shape and in some areas forming rosettes. The pathologic diagnosis was that of neuroblastoma. This was an extensive infiltrating neuroblastoma of the liver. No other primary site of the tumor could be found.

It was decided to give x-ray therapy which was considered palliative because of the critical condition of the infant. About 1,200 r tumor dose was given. The liver began to decrease in size. The patient began to eat well and to thrive.

Seven months later she looked like a normal healthy infant. The liver was now only two finger breadths below the costal margin. At this time a nodule was palpable in the left gluteal region. This was thought to be a metastasis of the original tumor. X-ray therapy was given to this area without any effect. The nodule was excised and we were happy to find that it was a foreign body granuloma which was apparently due to some of the injections that had been given.

It is now 3½ years since this child was in the

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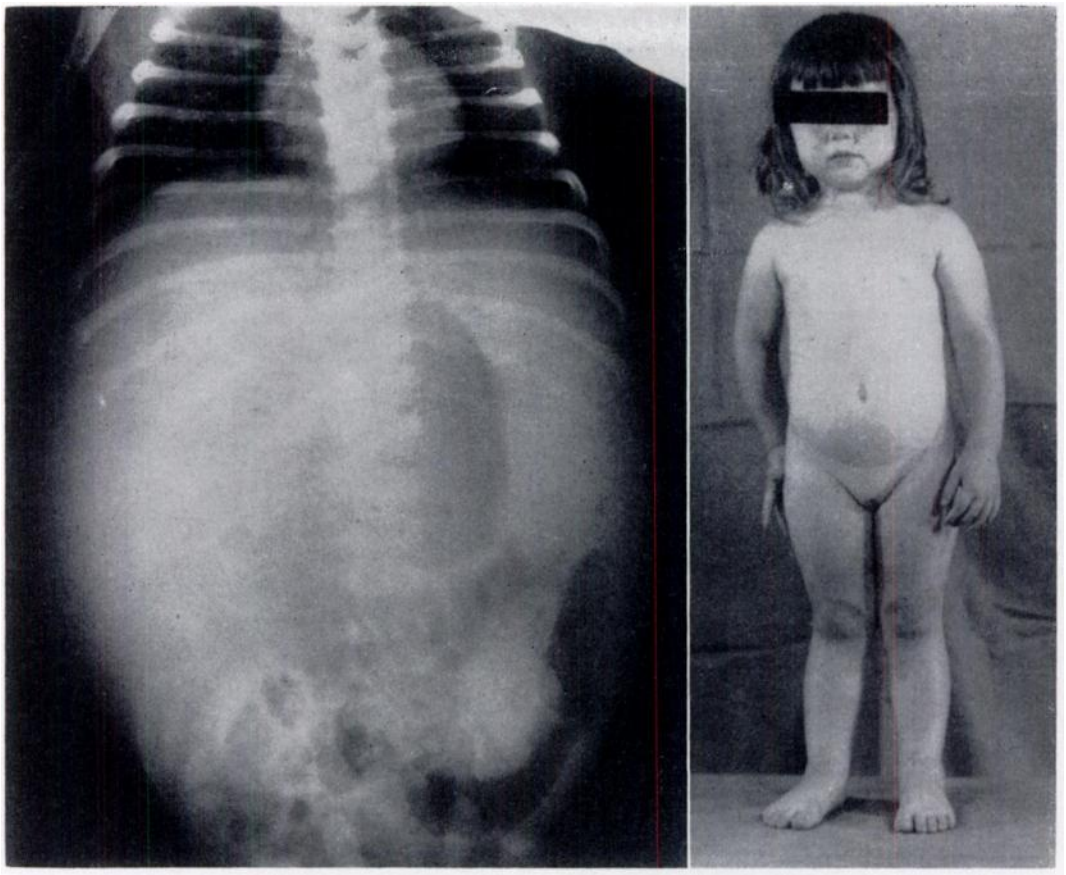

FIG. 1. (A, *left*) Patient K.S. with neuroblastoma of liver. Abdomen shows marked enlargement of the liver. (B, *right*) Same patient 3½ years after neuroblastoma found to be metastatic to liver. There is no evidence of tumor at present.

hospital with a neuroblastoma of the liver diagnosed at 5 weeks of age (Fig. 1, B). As you can see she appears to be completely normal. The liver is not palpable. How different the prognosis now as compared to the one expected for this patient when first seen at the age of 5 weeks.

Many of you heard the statistics presented by Dr. Gross (PEDIATRICS, **23**:1179, 1959) at this session of the Academy meeting in which he gave a rather favorable prognosis in neuroblastoma with liver metastasis. He stated that, from his experience of 217 cases, if there is no recurrence within 24 months you can probably be pretty sure the child is going to get well. This patient's prognosis is good but as the theme of my talk is to never make a positive prognosis I will say that we are 99% sure of a cure.

Wilms' Tumor. T.P., the next child I would like to present was 4½ years old when he entered our hospital. Four weeks before admission he had had what seemed to be a ruptured appendix. We have seen four such cases of Wilms' tumor mimicking appendicitis. Most had been operated upon before entering our hospital but we have done one ourselves, so we can't be too critical.

Four weeks before, the patient began to exhibit fever. He developed right abdominal pain and then developed a mass. He underwent exploratory laparotomy. A rather large mass was found which was called an abscess. This was incised and some necrotic material and blood drained out. A drain was put into the mass and the abdomen was closed. The child did very poorly and had pulmonary complications postoperatively. He was transferred to this hospital on August 31, 1955.

On physical examination the child was extremely emaciated and almost moribund. A huge nodular mass about twice the size of the

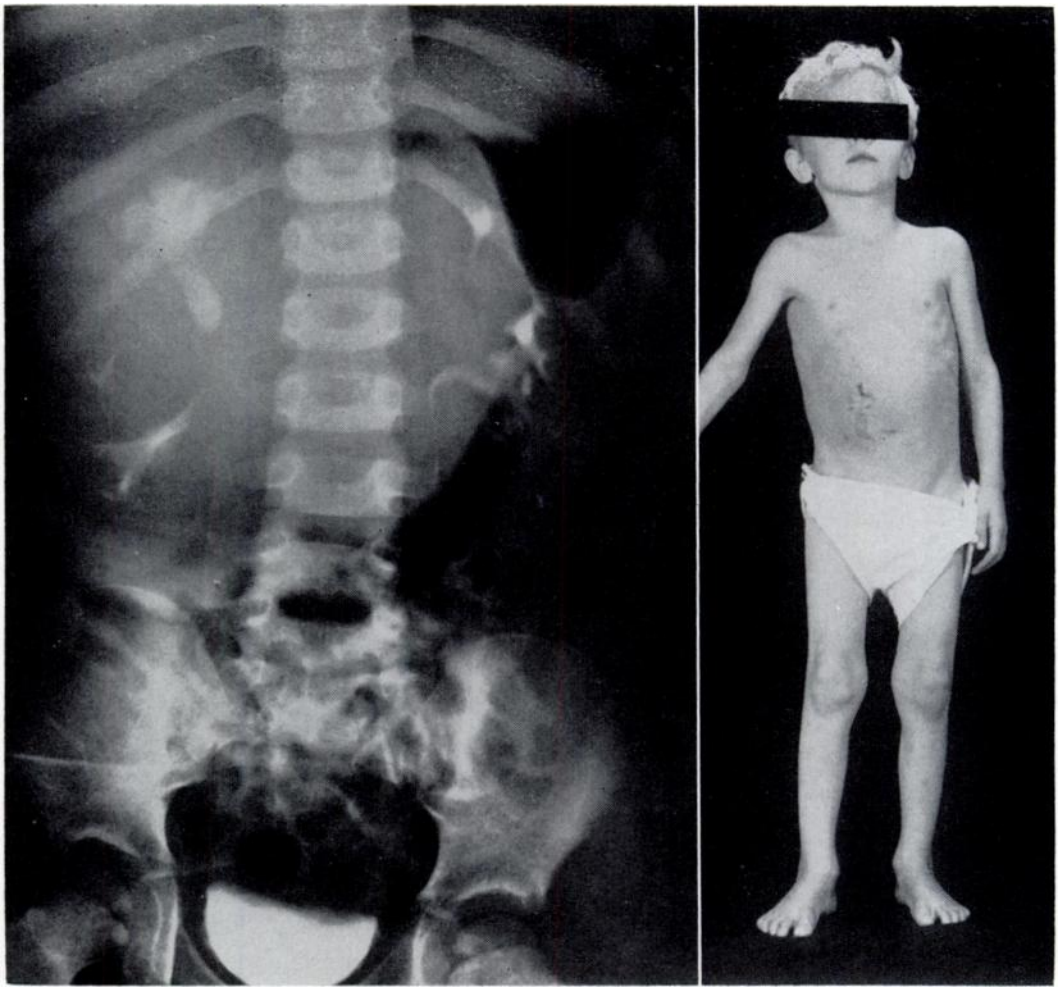

FIG. 2. (A, *left*) Patient T.P., with Wilms' tumor. Intravenous pyelogram shows a soft tissue mass in the right abdomen crossing the midline. The right renal pelvis is distorted. (B, *right*) Same patient before excision of the tumor. The Wilms' tumor had been "incised and drained." X-ray therapy had decreased the size of the tumor markedly.

child's head was noted in the right abdomen. There was dullness over the right lower chest and some rales.

Examination of the urine was normal. The erythrocyte count was 5,000,000/mm^3 and the hemoglobin was 12 gm/100 ml. This was undoubtedly due to hemoconcentration. The leukocyte count was 42,000/mm^3 with 77% polymorphonuclears. Intravenous pyelograms revealed a huge mass in the right abdomen distorting the right kidney pelvis (Fig. 2, A). Roentgenogram of the chest revealed an infiltrate of the right lung, which was interpreted as a possible metastasis or pneumonia.

We had therefore three rather dismal factors to consider. The first was that this child was in the older age group in which the prognosis may not be good. Second, the tumor was very large and had been "incised and drained." We were sure the peritoneal cavity had been well seeded with the tumor cells. Lastly, there was a possibility of a metastasis in the lung. Because of the size of the tumor and because of the rather poor outlook, we advised x-ray therapy in an attempt to shrink the mass and also to see how the child would do. X-ray therapy was given through three ports varying between 3,000 r and 3,900 r—a rather good size tumor dose, I believe.

The size of the mass decreased till it became one-third the size it had been, and the child gained 2.7 kg in weight (Fig. 2, B). It also

seemed apparent on follow-up roentgenograms of the chest that the lung findings had been due not to metastasis but rather to a pneumonitis that occurred after the first operation.

Therefore, with this minor encouragement we decided to operate; 6 weeks later the tumor was removed. There were no glands involved and no peritoneal seeding of the tumor.

The pathologic diagnosis was Wilms' tumor of the kidney with necrosis and radiation changes. There was no tumor invasion of the renal parenchyma. Tumor cells were seen in the renal hilar vessels.

It has been 3 years since the operation and we have waited with baited breath. As you can see he has continued to be the picture of health. Roentgenograms of the chest at 6-month intervals have been normal. There has been no evidence of metastasis to any part of the body. He really has done very well. His activities have been those of a normal boy.

We think the prognosis in this boy, who has gone for 3 years, is much more favorable than it was at the time of surgery. We are afraid we were a little brutal to the family about the prognosis at first because of all the complications. We can be a little happier about his prognosis now though he certainly is not out of the woods. We would rather have a follow-up of another 2 years, but at the present time we can probably say that he has a pretty good chance of surviving without any more trouble.

Acute Lymphatic Leukemia. The next patient is a very interesting child, unique in our experience, especially because of the type of tumor he presented. E. K. was nearly 3 years old when he came to the hospital on August 30, 1952. In the history it was stated that he had been pale for 1 week. For some months he had been drinking 2 quarts of milk daily and had eaten no meat, fruits or vegetables.

The family history was non-contributory. There was a female sibling 11 years of age.

On physical examination he was of normal weight but very pale and lethargic. The liver was down ½ in. and the spleen not palpable. There was no significant lymphadenopathy. The concentration of hemoglobin was 2.8 gm/100 ml; erythrocytes, 1,340,000/mm^3. The leukocyte count was 3,050/mm^3 and the differential count, polymorphonuclear leukocytes 21%, lymphocytes 65%, monocytes 13% and eosinophils 1%.

The patient was thought to have a nutritional anemia. He was given four blood transfusions and an oral iron preparation. Upon discharge the hemoglobin was 7.9 gm/100 ml, erythrocytes 2,140,000/mm^3 and the reticulocyte count 1.3%.

He was readmitted 1 month later with a history of having had a fever of 37.8-39.4° C daily for 10 days, a poor appetite and a few loose stools. He appeared chronically ill, was very pale and there was apparent weight loss. The liver was enlarged three finger breadths and the spleen was very firm and palpable four finger breadths below the right costal margin. There was generalized lymphadenopathy. No ecchymotic areas were present. The abdomen was soft and not tender.

The concentration of hemoglobin was 4.8 gm/100 ml; erythrocytes, 1,760,000/mm^3; leukocytes, 4,950/mm^3. The reticulocyte count was 0.1%. The platelet count was 55,000/mm^3. Ninety-eight per cent of the leukocytes were lymphocytes and 2% polymorphonuclear.

On examination of the bone marrow all the leukocytes were of the lymphocytic series. Most of these were vacuolated lymphoblasts. Erythrocyte maturation was markedly reduced and no megakaryocytes were seen. A second bone marrow examination 2 weeks later was similar. A diagnosis of acute lymphatic leukemia was made.

Administration of ACTH, 100 mg daily, was started. He continued to have a fever up to 40°C daily for 3 weeks. Twelve days after admission the abdomen became distended and continued so, although there was no muscle rigidity. There was, however, some indefinite tenderness on the right side. Four weeks after admission a large appendiceal abscess was diagnosed. The ACTH was discontinued and the temperature spiked to 40°C daily thereafter. Upon palpating the abdomen before surgery the abscess could be felt to rupture. In a few hours the boy was in shock. At surgery the ruptured appendix was removed and over 1,000 ml of pus was removed from the abdomen. Recovery was fairly rapid and he was discharged from the hospital in about 4 weeks.

Two weeks before surgery for the appendiceal abscess there was marked improvement in the bone marrow; megakaryocytes were still reduced but platelet activity was active; the ratio of erythrocytes to leukocytes was still lagging, but very few blast cells were present.

There was also steady improvement in the peripheral blood count so that on discharge the platelet count was 454,000/mm³; erythrocytes, 4,070,000/mm³; hemoglobin, 11.4 gm/100 ml; and the reticulocyte count, 2.2%. The leukocyte count was 20,450/mm³ with 60% polymorphonuclears, 30% lymphocytes and 10% monocytes; 6% young forms.

The original bone-marrow smears have been examined by several hematologists and they all came up with a diagnosis of acute lymphatic leukemia. In the intervening 6 years many repeat bone marrow smears have been examined and all reported normal. Also, numerous blood counts have been done and all have remained normal. Since the original ACTH therapy there has been no treatment for the leukemia.

At the end of 2½ years, when we were beginning to doubt the diagnosis of acute lymphatic leukemia, a swelling appeared in the left testicle. This was excised forthwith and a microscopic section showed a lymphosarcoma or a leukemic infiltrate in the testicle. An examination of the regional nodes was negative. The inguinal and iliac nodes were resected, but there was no evidence of tumor cells.

We would remind you that it has been 3½ years since the testicular infiltrate was removed. It is a total of 6 years since the onset of his disease and the first diagnosis. We think he looks very well, all things considered. He has had no anemia since then. He has been perfectly healthy and has done what everybody else his age would do, and probably more. He has been examined very recently in the hematology department and has been given a clean bill of health.

We might say that the slides were reviewed by various pathologists throughout the United States because of the rather unusual nature of this case, and the pathologists all agreed that they would have to make the same diagnosis if they had been presented with the same case.

We are not saying that all of these cases are examples of cures. We think perhaps the first one is. The second patient is not out of the woods yet. The third one—well, we have no basis on which to establish anything because we have never seen a case exactly like this. We merely wish to emphasize, however, that no matter how gloomy the outlook, a 100% fatal prognosis should never be given. To say that a child will die, and that there is nothing more that can be done, will often drive the distraught parents to the door of the charlatan.

Neuroblastoma. A good example of such an occurrence is the following case. K.J. was a female infant 1 year of age when first seen by us. A mass in the abdomen had been reported 12 days previously.

Physical examination was negative except for a large, very firm nodular mass in the right abdomen which extended into the right pelvis. There were also firm, bean-sized right inguinal lymph nodes.

The erythrocyte count was 4,330,000/mm³; hemoglobin, 9.7 gm/100 ml; leukocytes, 4,900/mm³ with polymorphonuclears 42%, eosinophils 4%, lymphocytes 43% and monocytes 11%. The urine was normal. On roentgenographic examination there were calcifications along the paravertebral chains from the mediastinum to the lower abdomen. Intramuscular pyelograms revealed the kidney to be apparently normal but pushed downward and laterally.

A biopsy of the inguinal lymph nodes was characteristic of neuroblastoma, establishing the diagnosis without a doubt.

X-ray therapy was advised. The mother refused this. She decided that since there was such a hopeless prognosis she would rather go to the Hoxie Clinic, where the child was given goats' milk, vitamins and we don't know what else, after which they returned home. Serious marital difficulties developed over the type of medical treatment for the child. The father brought the child back to us 6 months later for the x-ray therapy that had been advised. The patient appeared very well except for the large abdomen. The same mass was present in the right abdomen but now smaller, very firm masses were also present in the left abdomen. On roentgenographic examination there were now additional calcifications laterally in the abdomen. There was no bone involvement. The blood count and urine were normal.

We were in the unenviable position of "Darned if you do and darned if you don't." If we give x-ray therapy and the child gets worse they will say, "See? The x-ray therapy did that. I knew we shouldn't have done it." If the child gets better with x-ray therapy they will say, "It was the Hoxie treatment that made the child well in spite of the x-ray therapy."

X-ray therapy to the abdomen was given 6 months after the child was first seen. When seen 6 months later, at the age of 2 years, she appears healthy. There is still a very hard

mass, lemon sized, in the upper right abdomen. No other masses are palpable and no metastases are present. The blood count is normal. We ought never put ourselves in the embarrassing position mentioned above. Rather than to say that a patient is hopeless, and to dismiss the case more or less from our minds, we should show parents kindness and understanding, and give attention to the comfort of the patient and the patient's general health. We should never snuff out that one little ray of hope, no matter how small it might be. For any one particular case it is always possible that the child may survive or that perhaps an anti-cancer drug may be developed which may be of benefit before the child dies.

Question: Dr. Riker, is the patient with leukemia now receiving an anti-metabolite?

Dr. Riker: He has had no treatment except for the ACTH given before development of appendicitis.

Question: Have you tried vitamin B_{12} in neuroblastoma?

Dr. Riker: Not with this patient, but we have used it in several others in doses as high as 20,000 μg/day. No apparent benefit was noted; all patients have died. I know Bodian suggested it. Some have reported results that are glowing and others that are not. There are spontaneous cures, and cures following x-ray therapy and after biopsy. I think it is very hard to evaluate any form of therapy without a rather large series. I don't think his series to date has been large enough or followed long enough to make us enthusiastic about treatment with vitamin B_{12}.

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