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Focal nodular hyperplasia of the liver after clomiphene treatment in a young boy

I MÓROCZ[1], Ilona BENKŐ[2], Cs KISS[2], Z BÁRSONY[2]

Institute of Pathology[1] and Department of Paediatrics[2], University Medical School, Debrecen, Hungary

The case of a 3.5-year-old boy treated unsuccessfully with clomiphene for cryptorchidism is reported. Nine months later focal nodular liver hyperplasia developed. Clomiphene promotes testicular descent by stimulating endogenous production of gonadotropins and their releasing factors. A causal relationship between the hepatic lesion and clomiphene treatment has been supposed. In our case subsequent fertility can only be expected from orchidopexy performed as soon as possible.

Hepatic function must be checked during and after clomiphene treatment also in children.

In childhood, liver tumours rank at the third place after Wilms tumour and neuroblastoma [8]. The most frequent form of liver tumours is hepatoblastoma (40%), followed by hepatocellular carcinoma (20%); adenoma and focal nodular hyperplasia (FNH) are rare (each 2%) in childhood [28]. The youngest reported case with focal nodular hyperplasia of the liver was a girl of four months [20]. Sweeney and Evans [27] described a five-year-old boy treated with a synthetic anabolic steroid for Fanconi anaemia in whom liver adenoma and focal nodular hyperplasia (FNH) developed simultaneously.

We report here on an almost 3 years old boy with bilateral cryptorchidism in whom FNH appeared nine months after clomiphene treatment.

Clomiphene stimulates gonadotropin secretion through the hypothalamo-hypophyseal axis, both by increasing the level of the releasing factors and by a direct effect on the pituitary [18], i.e. clomiphene replaces HCG and LH-RH in the treatment of testicular maldescent and has successfully been applied in cryptorchidism [4]. In gynaecology, clomiphene is used to measure the functional capacity of the hypothalamo-hypophyseo-gonadal system and to induce ovulation [13, 21]; it has also been applied for treatment of male infertility [1, 24]. Borderline carcinoma of the ovarium, due to too high levels of oestrogen provoked by overstimulation has been observed in clomiphene treated women [2]. The drug may play a part in the development of liver tumours: hepatoblastoma was seen in a 15 months old girl whose mother had been treated with clomiphene and follicle-stimulating and luteinizing hormones for infertility before conception [17]. In our case a causal relationship could be anticipated between clomiphene therapy and hepatic lesion.

Report of a Case

G. N., a boy, was born on 26 February, 1980, with 36 weeks gestational age and 2400 g birthweight. His mother was treated because of imminent premature labour with a total dose of 105 mg of allyloestrenol given on seven days in the 35th week of pregnancy. The newborn had prolonged jaundice due to AB0-incompatibility. His bilateral cryptorchidism was detected at birth. At the age of 3.5 years the child still had enuresis. He learned to speak with a considerable lag, he still speaks little and with errors. In December, 1982, he had been treated with 50 mg clomiphene daily over 20 days. By the end of this period his left testicle had become palpable in the inguinal canal, the right testicle could be pulled down from the inguinal canal into the scrotum, but it soon returned spontaneously to the initial site. Physical examination carried out before treatment revealed no abormality except the cryptorchidism. No liver function tests were performed prior to treatment. Nine months later the boy's parents had palpated an egg-sized painless tumour in the epigastric region. The child was admitted to our department. At admission, elevated GOT (135 U/l) and slightly increased serum bilirubin (21.6 μmol/l) were found. Abdominal sonography revealed an echo-rich region 3 cm in diameter in the left lobe of the liver; in addition, the left kidney seemed enlarged, its upper pole appeared to contain a solid structure. This made us to suspect a primary kidney tumour. Infusion urography, however, did not show any renal abnormality. Hepatic metastasis originating from a small Wilms tumour was then suspected and explorative laparotomy was carried out in September, 1983. A tumour 4 cm in diameter was excised in toto from the left lobe of the liver. The left kidney appeared tumour-free at surgery.

The tumour, measuring $7 \times 5 \times 4$ cm, was partly covered by peritoneum and contained a round, hyperplastic area, distinct from its environment but having no own capsule. The tumour was divided by irregular thin streaks into nodules of 0.5—1.5 cm. In the centre of the tumour a necrotic focus 1.2 cm in diameter was found.

The substance of the hepatocellular hyperplasia surrounded by slightly deformed liver tissue with normal trabecular pattern was divided by long collagen streaks which had in some areas a stellate shape (Fig. 1). In other areas the streaks surrounded nodules similar to those characteristic of a cirrhotic liver (Fig. 2). In the broad connective tissue septa lymphocytic infiltration accompanied by bileduct proliferation was seen (Fig. 3). The hyperplastic cells were large, had a polygonal shape, most of them were tightly joined but sparsely they formed pseudoglandular formations consisting of 6—10 cuboid or cylindriform cells (Fig. 4). No signs of atypia or malignancy were seen in the hyperplastic area, rarely binuclear cells could be encountered. No vascular changes were detected in the environment of the well-defined necrotic focus lying in the centre of the tumour-like lesion. The histologic diagnosis was hepatic nodular focal hyperplasia.

After an uneventful postoperative period the child was discharged. Laboratory tests were performed one week and one month after surgery; their results suggested gradual improvement: serum GOT: 45 and 15 U/l, respectively, serum GPT: 58 and 11 U/l, respectively, and serum total bilirubin: 6.5 μmol/l on both occasions.

Discussion

Benign focal nodular hyperplasia of the liver is a rare condition in childhood [25, 28]. The largest series, comprising 61 paediatric cases, collected by Stocker and Ishak [25] revealed a female dominance (72%); 41% of the cases were younger than 5 years. The condition is often accompanied

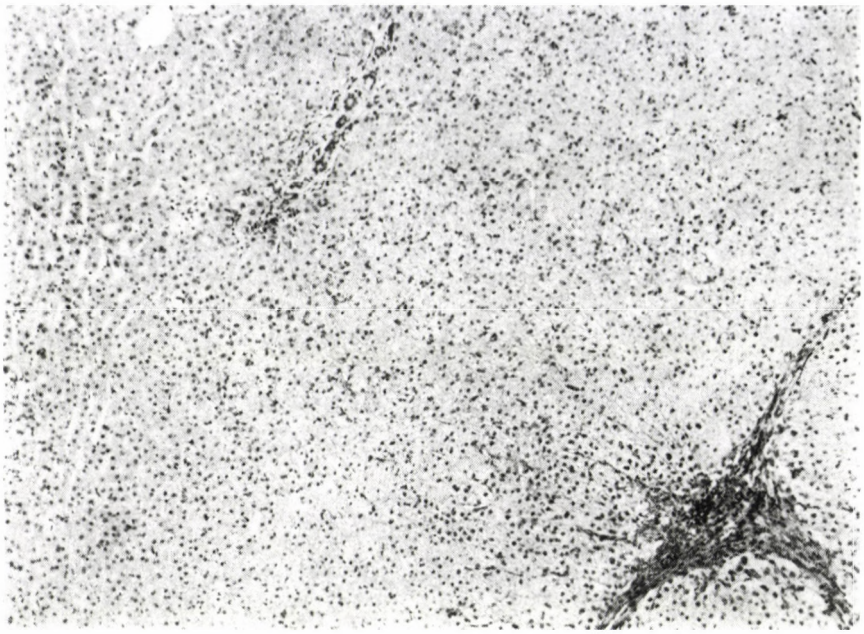

FIG. 1. Focal nodular hyperplasia of the liver, on the left margin hepatic tissue of intact structure. At the right bottom a star-shaped connective tissue streak (H & E, ×63)

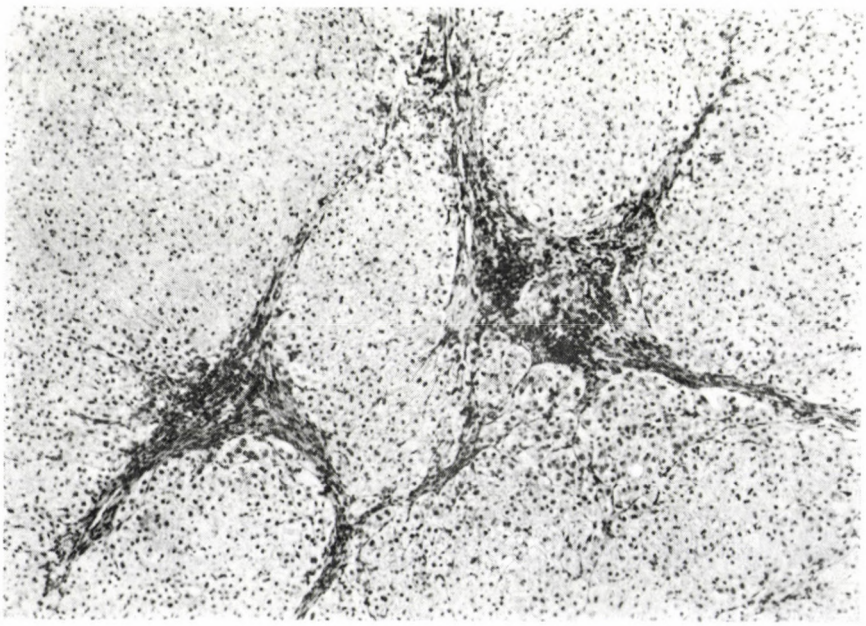

FIG. 2. Cicatrisant streaks with lymphocyte infiltration produce cirrhosis-like nodules within the hyperplastic area (H & E, ×63)

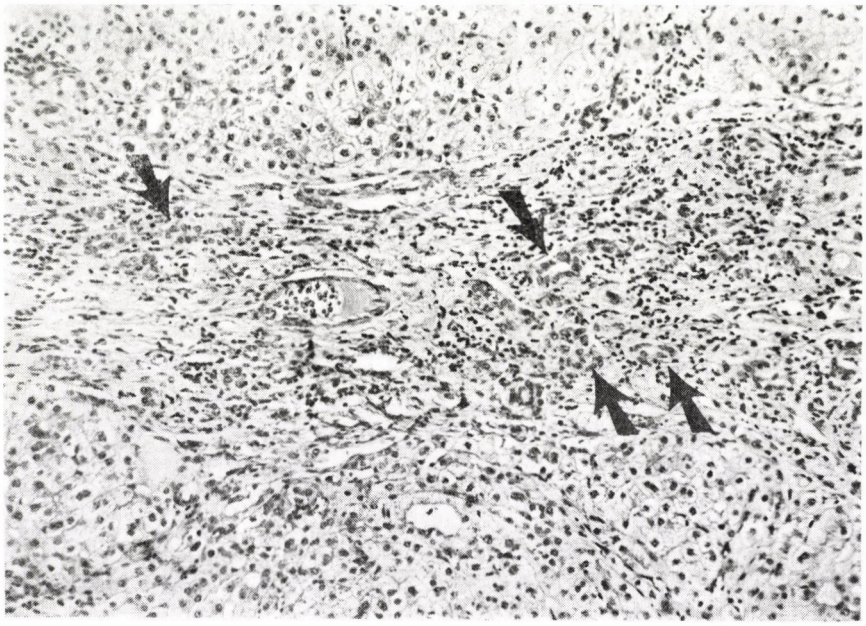

FIG. 3. Lymphocyte infiltration within the broad connective tissue septa, the arrows point to proliferation of bile-ducts (H & E, ×100)

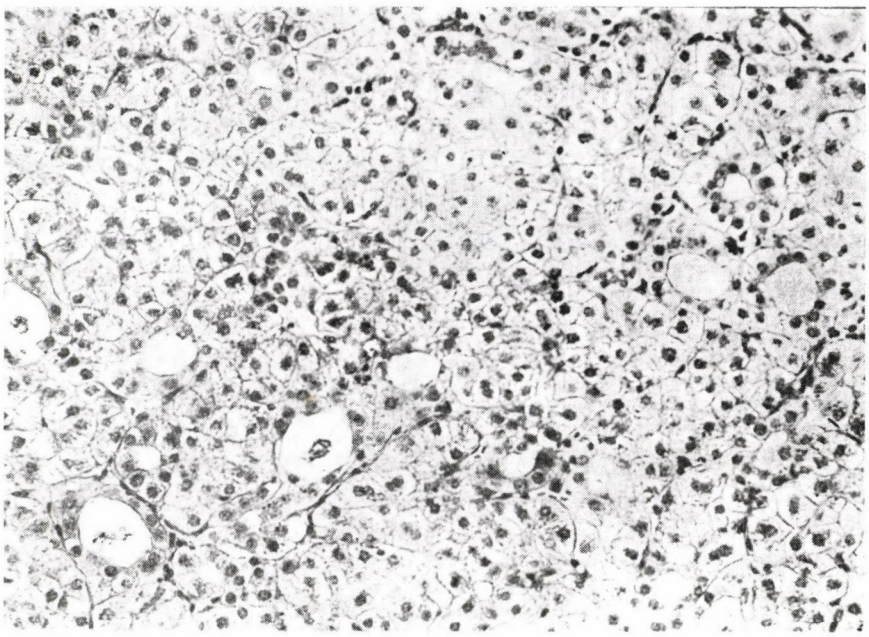

FIG. 4. Pseudoglandular formations of hepatocytes within hyperplastic nodules (H & E, ×160)

by other malformations: multiple teleangiectasis on the arms and legs [10], hypospadiasis, bilateral syndactyly of the toes and bilateral hydrocele, leftsided hemihypertorphy, multiple teleangiectasis over the face and the lips, and umbilical hernia [9]. Some are complicated by a metabolic disorder, type I glycogen storage disease [12]. Mones and Saldana [20] observed in a four-month-old girl Krabbe disease (autosomal recessive demyelinisation of the central nervous system) in addition to nodular regenerative liver hyperplasia. In our case no concomitant disorders could be detected. In cases treated with continuous androgen therapy for Fanconi anaemia the FNH could be ascribed to the drug [6, 27]. In women taking contraceptive pills the relationship between hepatic adenoma [3, 7] or focal nodular hyperplasia [15, 16] and the drug has firmly been established. This factor can, however, be excluded in the aetiology of FNH in childhood. Some authors regard FNH as a hamartomatous malformation [25, 28]. Others underlined the non-tumorous character of FNH by pointing out the structural changes in the blood vessel wall [15, 16, 25] and regarded the hyperplasia as regenerative [20, 26]. Malignant transformation of focal nodular hyperplasia of the liver has never been observed in paediatric patients [8, 25]. Its adequate therapy is surgical excision [25, 28]; no further treatment, cytostatics or irradiation are needed.

Clomiphene is a double-faced synthetic compound with weak oestrogen properties and void of an androgenic effect. Since it binds to the oestrogen receptors of the hypothalamic target cells, the drug deplaces the endogenous hormones with a stronger effect than clomiphene itself, thereby it has a seemingly anti-oestrogen effect as well [29]. As follows from the mode of action of clomiphene [19] the drug can replace HCG and LH—RH in the treatment of testicular maldescent by increasing the level of endogenous gonadotropin and by stimulating production of the releasing factors.

These considerations have led to the introduction of clomiphene in the hormone treatment of testicular maldescent [4]. In addition to an improvement of the testicular position, an increase in the LH and testosterone level have proved the efficacy of the drug [5].

For induction of ovulation, a 5-day course applying a total dose of 250—750 mg has been recommended [13, 21]. For treatment of male infertility daily 50 mg clomiphene on 25 consecutive days was recommended over one to six months, in a total dose of 1250—7500 mg [1]. Paulson [23] and Ross et al [24] reported on favourable effects while Abel et al [1] did not find any difference between the effects of clomiphene and vitamin C. If cryptorchidism is unresponsive to hormone treatment, fertility can only be expected if orchidopexy is performed as early as possible [11].

Hepatoblastoma developed in a 15-month-old girl born to a mother

treated with follicle-stimulating and luteinising hormones plus clomiphene for infertility over one year prior to her pregnancy [17]. As far as we know, this is the only proven case in which clomiphene had an aetiological role in the pathogenesis of a malignant liver tumour.

A role of hormone preparations taken by the pregnant mother in the pathogenesis of liver tumours appearing in her infant has been suspected by some authors [18, 22]. In our own case, the mother had been treated with allyloestrenol; this may have affected the hepatic function of the fetus, resulting in an altered reaction to subsequent clomiphene treatment of the child itself. Hormonal treatment of the mother, even before conception, but especially when administered inadvertently during the first weeks of pregnancy [18, 22] may affect liver function of the fetus and its sensitivity to potentially oncogenic substances.

Clomiphene treatment of cryptorchidism during childhood is based on the experience gathered in the therapy of adult hypofertility [23, 24]: it does induce production of endogenous hormones. However, caution is recommended in case of children as well: liver function has regularly to be checked.

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I Mórocz MD
P.O. Box 23
H-4012 Debrecen, Hungary