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OSTEITIS TUBERCULOSA FISTULOSA FOLLOWING VACCINATION WITH B.C.G. STRAIN

By

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This paper is concerned with progressive tubeculous osteitis of the talus due to spread of B.C.G. from the site of intracutaneous vaccination[1].

B.C.G.-vaccination has found extensive use and the vaccine has been administered to more than 100 million human beings in all parts of the world (*Griesbach* 1954, *Bloch* 1955, *Wallgren* 1955, *Irvine* 1955 and *Deinse* 1956).

It is widely believed that this vaccine can be administered without danger (*Irvine* 1949, 1954, *Griesbach* 1954 and *Mande* 1954) and that the problem is rather that the virulence of the B.C.G.-strains used may decrease and thereby fail to give sufficient protection against tuberculosis (*Heimbeck* 1932, *Wallgren* 1947).

It should, however, be borne in mind that B.C.G. is not an avirulent but rather an attenuated strain (*Jensen* 1946, *Dubos* 1955, *Deinse* 1956, *Ustvedt* 1956, *Wallgren* 1957), as is obvious from the high frequency of takes (*Lindau* 1955).

As to the complications of B.C.G.-vaccination, local abscesses and regional lymphadenitis may develop though not often. In newborns, in whom the natural resistance is low, a relatively large dose of vaccine prepared from cultures harvested early, may, however, produce such changes occurring with a frequency of anything up to 25 per cent (*Guld, Magnus, Tolderlund, Biering-Sörensen & Edwards* 1955).

These local reactions are not followed by any permanent sequelae.

A more troublesome local reaction is the development of lupus-like skin lesions round the site of injection. Such untoward reactions were

[1] Delivered before Orthopaedic Congress in Stockholm.

first reported by *Kristjansen* (1944, 1945) in a case described later also by *Lomholt* (1946) and *Jensen* (1948).

This reaction has since been described by *Bruns* (1949), *Kalkoff* (1950), *Gilje* (1952), *De Bruijne* et al. (1952, 1953), *Marcussen* (1953 1954), *Imerslund & Jonsen* (1954), *Macharáček & Tesař* (1954), *Ødegaard* (1954), *Marie* et al. (1955), *Horwitz* (1955), *Davies* (1955), *Šula* (1955), *Høvding & Wetteland* (1956).

Of much greater importance, however, are the 4 cases of generalized fatal complications of B.C.G.-vaccination reported in recent years in Scandinavia. It appears that these are the only 4 cases on record.

Meyer (1953, 1954) described a child, who had been vaccinated with B.C.G. at the age of 7 years and afterwards developed multiple suppurating adenitis (malignant form of scrophulosis). The patient died from cachexia 2 years later. (Microbiologic studies by *Jensen*, 1954).

Hollström & Hård (1953) described a patient who was vaccinated with B.C.G. soon after birth. Local unceration and regional lymphadenitis with suppuration was followed by lymphoglandular spread. The patient died, and postmortem examination showed a picture resembling miliary tuberculosis.

Thrap-Meyer, Oeding, Hesselberg & Waaler (1954) described the third known fatal case. The patient was a 24-year old man who, four and a half years after vaccination, developed multiple foci in the skeleton, lymph nodes and lungs as well as ulceration of the rectum and urinary bladder. Marasmus, fistulation and paraparesis supervened and the patient died.

Falkmer, Lind & Ploman (1955) described a fatal complication of B.C.G.-vaccination. The patient, who had been vaccinated soon after birth, died at 8 months from progressive generalized tuberculosis.

In all of these cases culture gave growth of bacilli indistinguishable in morphology or pathogenecity from B.C.G.

Of possible greater relevance is a small group of cases on record, in which B.C.G. had evidently spread via the blood stream but resulted in only isolated foci of surgical tuberculosis, and in which the course was relatively benign. These cases with circumscript foci are described in brief below:

Génévrier & Maclouf (1948) reported on a 20 year old girl who one month after B.C.G.-vaccination in the lumbar region (scarification) developed an abscess in the right breast. Culture of aspirated fluid (L' Institut Pasteur) showed bacilli of B.C.G.-type. No other foci were

demonstrable. Treatment consisted of repeated aspiration only, and the abscess healed within 8 months.

Öster (1953) described a patient, who had been vaccinated in the left shoulder at 2½ years of age. Fourteen months after vaccination a subcutaneous abscess appeared on the lateral aspect of the right knee. Roentgen examination of the knee showed no signs of a pathologic condition. No other foci were observed. The abscess was extirpated. Culture gave growth of bacilli of B.C.G.-type (Statens Seruminstitut, Copenhagen). The wound healed in 2 weeks without complications. The patient's general condition had been good throughout. On review 8 months later the patient felt well and physical and roentgen examination revealed nothing of interest.

Imerslund & Jonsen (1954) described a patient who had been B.C.G.-vaccinated at 4 weeks of age. Six months later, following measles, the vaccination mark began to increase and 3 months later a lupus-like lesion appeared with regional adenitis in the left axilla. Roentgen examination 2 years after the vaccination showed destructive foci in as many as 5 bones: enlargement and thinning (spina ventosa) of the first right metatarsus, a lesion in the proximal part of the right ulna and foci in the eighth thoracic vertebra and third and fifth lumbar vertebrae.

Chest X-ray showed nothing of interest. The patient was in a good general condition. The tuberculin reaction (0.1 mg.) was positive. Culture of material from an abscess in the metatarsal bone gave growth of bacilli of B.C.G.-type (*Svenkerud* 1955). Similar growth was obtained on culture of material from the skin lesion. The patient received chemotherapeutics and the foci in the metatarsal bone were excochleated. The osteitis proved fairly benign. When last seen about 3 years after vaccination the patient felt well and roentgen examination showed regression of the bone lesions.

Mørkbak (1954) described a girl who had been vaccinated with B.C.G. and after chicken pox, developed at 7 months osteomyelitis with fistulation in the distal part of the right ulna. The lesion was excochleated. Pathologic examination showed tuberculous granulations. Culture (Statens Seruminstitut, Copenhagen) gave growth of bacilli of B.C.G. type. Mantoux (0.1 mg.) was positive. The patient received streptomycin first after the operation but not INH. On roentgen examination one year after operation the ulna was found to be somewhat shorter and thicker than on the other side but the structure of the bone was normal.

The literature also contains other cases of progressive tuberculosis following vaccination with B.C.G., in which, however, it is questionable whether the vaccine was the causal factor, and which are therefore not considered here.

REPORT OF CASE

A girl, aged 2½ years (born 24 September 1951) was admitted to the Department of Orthopaedic Surgery, University of Lund, on April 8, 1954. She was the second of 3 siblings and did not come from a poor home. The other members of the family had always been healthy. She had not been exposed to any known open tuberculosis. The father was a fisherman, and reported that an appreciable part of the family's diet consisted of fish.

The patient had been vaccinated with B.C.G. intracutaneously on the outer side of the left thigh at 3 days of age. The dose administered was 0.05 mg. of B.C.G. Vaccination was not followed by any complications. Mantoux-test on December 7, 1951, with 1.0 mg. of tuberculin was negative. The tuberculin test was repeated 14 days later with the same dose and with the same negative result.

The patient was therefore vaccinated a second time intracutaneously on the outer side of the left thigh on Jan. 22, 1952, this time also with a dose of 0.05 mg. Nor this time was the vaccination followed by any immediate complication. The Mantoux-test on April 10, 1952, was positive.

The district nurse who had performed the re-vaccination and the Mantoux-test reported that she had never observed any complications after B.C.G.-vaccination in her district.

In May to July, 1953, the patient had uncomplicated whooping cough and a "sore throat" in December that year.

On March 19, 1954, the patient's mother noticed for the first time that the girl walked with a limp. She also observed that the left foot and ankle were swollen and tender. The patient complained of ankle pain even when resting. The pain was most intense at night and sometimes disturbed the patient's sleep. The girl was listless and tired. Body temperature was not measured.

She was later admitted to her local hospital, where roentgenography of the foot on March 23, 1954, revealed no signs of a pathological condition. Later check-inspection of these roentgenograms, however, now showed a rounded rarefaction about 3 mm. in diameter in the talus.

On admission to the Department of Orthopaedic Surgery the girl was found to be of normal development and well nourished. She was somewhat pale. Physical examination (heart, lungs, abdomen) revealed nothing of interest. She refused to stand on the left foot. Around the left ankle was a reddish, warm, fluctuant tender swelling, particularly along the anterior margin of the lateral malleolus. All movements of the ankle were markedly limited and painful.

Body temperature was 37.3° C on admission, but on the following day it rose to 40.2 after the abscess had been punctured through healthy tissue. About 2 ml. of yellow blood-stained fluid was produced.

Mantoux (0.05 mg.) was positive. The micro-erythrocyte sedimentation rate on admission was 26 mm./1 hour. Hb 70 %, R.B.C. 3,480,000 per c.mm., W.B.C. 4,800 per c.mm., Diff.: N. 58 %, E. 1 %, B. 0 %, L. 39 %, M. 1 %. Immature monocytes 1 %.

Roentgen examination showed: sclerosis of the left talus, erosion of the posterior part of the talus and rarefaction of all the foot bones. (Fig. 1).

Chest X-ray revealed nothing of interest.

No other lesion could be demonstrated in the lungs, or elsewhere during the later course of the disease either.

Since vaccination had not been followed by any primary complications, the lesion was not interpreted as being of tuberculous origin. Penicillin therapy was therefore started. The lower leg was placed in plaster. Within 2 weeks the body temperature was almost normal.

Gradually a fistula developed in the medical side of the ankle joint.

Roentgen examination showed an increase in the size of the defect in the talus.

Material from the abscess was sent to the Bacteriological Institute in Lund. Culture on blood plate and in browth gave no growth. Löwenstein culture of sample No. 1 (taken on April 9, 1954) gave scanty growth of acid-fast rods. The morphology of the colonies resembled tubercle bacilli of human type. The guinea-pig test was, however, *negative*.

On May 28, 1954, a second sample (sample No. 2) was sent to the Bacteriological Institute. Culture on Löwenstein medium gave growth of a few colonies of acid-fast rods. The morphology resembled that of tubercle bacilli of human type. The guinea-pig test was again negative.

The possibility of B.C.G.-infection was suspected. The culture from sample No. 2 was therefore sent to K. A. Jensen, Copenhagen, and to A. Lind, Gothenburg, for special investigation. Jensen arrived at the conclusion that it was definitely a case of B.C.G.-infection[1], while Lind stated that the bacteria could not be distinguished from B.C.G.[2]. It should be observed that before collection of sample No. 2 the only antituberculosis treatment the patient had received was INH mg. 75 daily for 3 days.

On June 1, 1955, the electrophoretic serum protein pattern showed slight reduction in albumin, slight increase in α_2 and β_2 globulins, but nothing else of interest.

The patient was treated with INH and streptomycin, and on September 13, 1954, the lesion was excochleated and the bone defect was filled with INH and streptomycin.

Histologic examination of the tissue removed showed a picture of the type seen in tuberculous inflammation, though no acid-fast rods were demonstrable.

Repeated check-radiography showed no further increase in the size of the lesion and the density of the bones around the defect gradually increased. The fistula, however, remained open and the ankle remained swollen and tender.

It was therefore decided to reoperate (September 29, 1955). Via an incision over the anterior aspect of the ankle, a hole was chiselled in the upper surface of the

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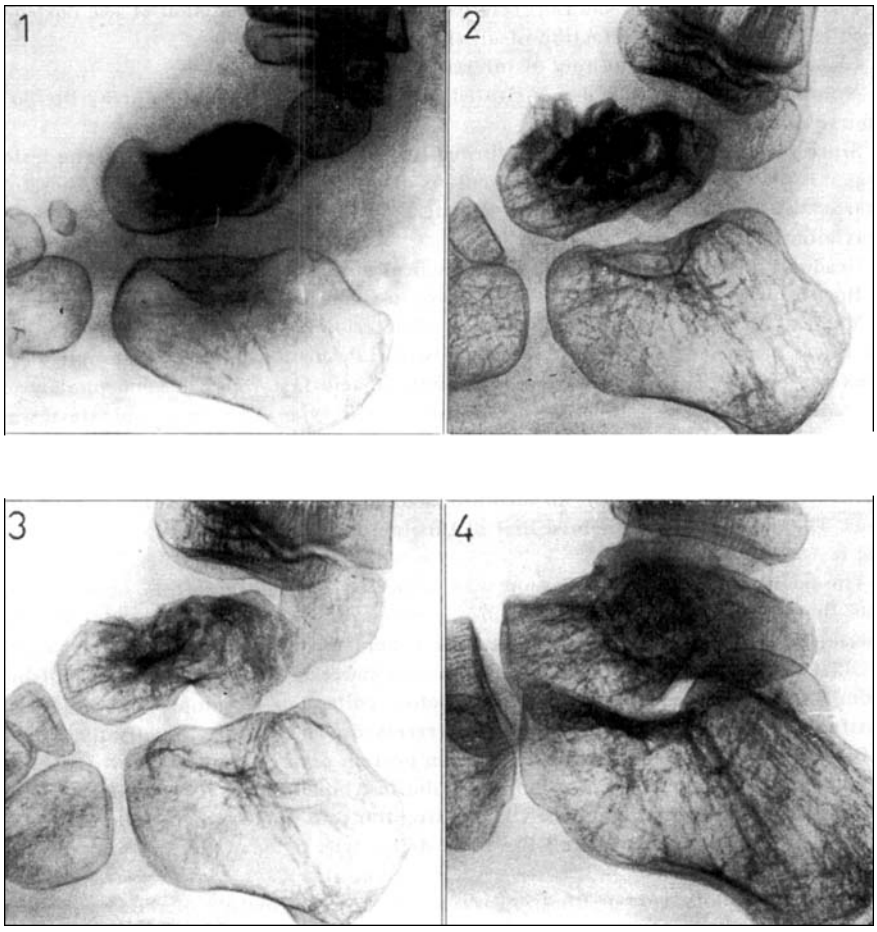
[1] *K. A. Jensen* reported that there was hardly any doubt that the culture he had received was a B.C.G. strain. It did not grow in Besredkas substrate, and on subcutaneous injection into guinea-pigs it produced the same changes as injection of the same doses of B.C.G.

[1] *A. Lind* reported that on postmortem examination 75 days after inoculation the guinea-pigs showed no gross tuberculous changes. The strain did not grow on Besredkas medium and gave no change in colour on culture on Eier-Lockemann-medium substrate with bromcresol purple. The culture could not be distinguished from B.C.G. except in its resistance which may have been due to treatment of the patient.



neck of talus. After excochleation of the lesion, which was found to consist of greyish granulation tissue and sequestrated bone, INH and streptomycin were dieposited in the cavity. The cavity was then filled with bone chips. (Fig. 2).

The patient's general condition was good throughout. On examination 9 months after admission the temperature was normal and after 11 months the E.S.R. was also normal. During this time the girl was bright and cheerful, her appetite was good, she slept well and developed in a normal way.

The fistula healed soon after the last operation. When sent home in November, 1955, (1 year and 8 months after discovery of the disease) the swelling and tenderness around the ankle, which was still in a rigid splint, had almost disappeared. She still walked with a slight limp but was otherwise free from symptoms.

At the review on March 12, 1956, (2 years after onset of dicase) roentgen examination showed further improvement in the trabecular structure in the talus. (Fig. 3).

At the last review on November 7, 1958, (4½ years after onset of disease) the patient was almost symptomfree. The range of movement of the ankle and subtalar joints were, practically speaking, normal.

Roentgen examination showed the bone structure of the talus to be practically normal. The trochlea of the talus was somewhat flattened. The foot bones were still somewhat rarefied. (Fig. 4).

DISCUSSION

As known, B.C.G.-vaccination is rarely attended by serious complications.

The few reports of serious complications may probably be ascribed to decreased natural resistance of the patients (*Hollström & Hård* 1953, *Imerslund & Jonsen* 1954, *Oeding & Hesselberg* 1954, *Falkmer, Lind & Ploman* 1955, *Irvine* 1955, *Wallgren* 1955, 1956, 1957, *Lindau* 1956, *Gehrels* 1956, *Groth-Petersen* 1956, *Weingärtner* 1957 and others).

It is known that in experimental animals with decreased resistance B.C.G.-vaccination may be fatal. Guinea-pigs will, as a rule, survive. However, if the resistance of such an animal is lowered by experimental silicosis (*Vorwald, Dworski, Pratt & Delahant* 1950) or deficient diet (*Dubos* 1954), B.C.G.-inoclulation is capable of producing progressive fatal tuberculosis. *Vorwald* et al. (1950) also showed that the fatal outcome was due to the experimental pre-existing pathologic condition of the experimental animals and not to any enhancement of virulence of the B.C.G. bacilli inoculated.

Wallgren (1955) discussed the possibility of agammaglobulinaemia favouring the development of progressive tuberculosis following B.C.G.-vaccination in human beings. Neither in any of the above mentioned 8 cases of progressive tuberculosis in the literature following spread of B.C.G. nor in the present case was any such agammaglobulinaemia found (see above).

Lindau (1956) expressed the view that the period between the second and seventh month of life is less favourable from an immunobiological point of view. During that period the antibodies transferred passively from the mother have disappeared and the production of gammaglobulin by the infant is yet slight. *Parkes* (1958) speaks of physiological deficiency of gammaglobulin found in infants aged 4–12 months. He described two cases of tuberculosis associated with hypogammaglobulinaemia in adults and arrived at the conclusion that the natural course of tuberculous disease appears to be unaffected by hypogammaglobulinaemia.

Of the above mentioned 8 cases of progressive tuberculosis due to B.C.G., 4 of the patients had been vaccinated around the above-mentioned period with slight antibody production namely those of *Hollström & Hård* (1953), *Imerslund & Jonsen* (1954), *Mørkbak* (1954) and *Falkmer, Lind & Ploman* (1955). To these may be added the case described in this paper. These few cases do not permit any valid conclusions as to whether the age period is less suitable for vaccination with living agents. However, it appears desirable that this question receive more attention in a larger material.

It has been claimed by various workers in this field that living B.C.G. may often spread from the site of injection. Animal experiments, suggesting this, have been performed by *Ström & Rudbäck* (1949), *Spiess* (1953), *Sternberg & Frappier* (1955) and others, who worked with labelled (mainly P^{32}) B.C.G. vaccines. They found a rapid spread of the radioactive substance throughout the body after injection of B.C.G.

More direct evidence of haematogenous spread of B.C.G. with formation of small regressive foci in various parts of the human body after vaccination is apparent from the histologic examination of *Gormsen* (1956) in association with medico-legal autopsies of B.C.G. vaccinated human beings. In 13 of 20 persons who had suddenly died from various conditions 6 weeks to 40 months after B.C.G.-vaccination he found signs of lesions in the inner organs suggesting haematogenous spread of B.C.G. that had, however, not produced any manifest disease. He gave no bacteriologic evidence of these lesions being due to B.C.G., but other evidence in favour of such an assumption must be regarded as strong (*Ustvedt* 1956).

In the present case the patient had apparently been vaccinated in and adequate manner. Other persons who had been vaccinated with material from the same batch developed no alarming complications. In addition, subcultures of bacilli from the patient could not be distinguished from B.C.G. in virulence in guinea-pigs either. All this argues against the osteitis having been due to inadequate vaccination or to too virulent a vaccine.

As to any lowering of the patient's natural resistance to the inoculated B.C.G.-organisms, the patient was, as mentioned, re-vaccinated within the period described by *Lindau* as being less suitable because of the slight antibody production.

During hospitalization the gammaglobulin was not found to be abnormally low (electrophoresis 2 years, after onset of disease). Neither

did other laboratory studies or clinical observations suggest impaired natural resistance. This does not, however, exclude the possibility of factors influencing resistance having escaped notice, especially during the period before admission of the patient to hospital.

Judging by the cases on record in the literature, in which the skeleton was involved, B.C.G. thrive well in bone tissue.

In the present case, the lesion ran a relatively benign course as in other cases on record with circumscript foci of surgical tuberculosis due to spread of B.C.G. via the blood stream.

SUMMARY

B.C.G.-vaccination is rarely attended by serious complications.

In addition to the commonest complications, local abscess and regional lymphadenitis, lupus-like skin lesions around the site of injection have been described in a few cases.

Four cases of generalized B.C.G.-lesions, all fatal, are on record in the literature.

Four cases have been reported in which haematogenous B.C.G. spread has occurred but given rise to only a few isolated lesions of surgical tuberculosis.

In the present case, a girl was vaccinated with B.C.G. intracutaneously on the left thigh at the age of 3 days and again at 4 months. At 2½ years she was found to have fistulating tuberculous osteitis of the left talus. Bacteriologic examination showed that the osteitis was due to B.C.G., which must apparently have spread haematogenously from the site of vaccination. No other foci were found. Four and a half years after the onset of the disease the patient was symptomfree and roentgen examination showed practically no signs of a pathologic condition.

The patient had been vaccinated in an adequate manner with vaccine from a batch that had not produced complications in other persons. Subcultures of the bacilli showed typical virulence on injection into guinea-pigs.

No signs of decreased resistance were observed while the patient was in hospital. Nevertheless, the only explanation available for the disease was decreased resistance to B.C.G.

The patient was re-vaccinated during a period of life when gammaglobulin production is low.

RESUME

La vaccination au B.C.G. donne rarement lieu à des complications graves.

En dehors des complications les plus communes, des abcès locaux et des lymphadénies régionales, des lésions de l'epiderme ressemblant au lupus autour de l'endroit où a été pratiquée l'injection, ont été décrits dans un petit nombre de cas.

Quatre cas de lésions B.C.G. généralisées, toutes suivies de décès, sont enregistrés dans la littérature.

Quatre cas ont été rapportés dans lesquels la propagation hématogène du B.C.G. n'a donné lieu qu'à quelques lésions isolées de tuberculose chirurgicale.

Dans le présent cas, une fille a été vaccinée par injection intradermique sur la cuisse gauche à l'âge de 3 jours et une fois encore à l'âge de 4 mois. A 2 ans et demi, on découvrit qu'elle avait une ostéite tuberculeuse à fistules dans le talon gauche. Un examen bactériologique montra que l'ostéite était due au B.C.G. qui, apparemment, s'était propagé hématogéniquement du côté de la vaccination. Aucun autre foyer n'a été découvert. 4 ans et demi après la découverte de la maladie, la patiente n'avait plus aucun symptôme et, à l'examen radiographique, il n'y avait pratiquement plus aucun signe de l'état pathologique.

La malade avait été vaccinée de la manière appropriée, avec du vaccin provenant d'un lot qui n'avait provoqué aucune complication chez d'autres. Des cultures de bacilles ont montré une virulence typique à l'injection chez des cobayes.

Aucun signe de résistance afaiblie n'a été observé pendant que la malade était à l'hôpital. Néanmoins, la seule explication plausible à la maladie est une résistance affaiblie au B.C.G.

La malade a été vaccinée à nouveau à une période de la vie où la production de gamma-globuline est faible.

ZUSAMMENFASSUNG

Ernstliche Komplikationen im Zusammenhang mit der B.C.G. Impfung sind sehr selten.

Abgesehen von der häufigsten Komplikation, der örtlichen Abszessbildung und regionären Lymphadenitis, wurden Lupus-artige Hautprozesse and der Injektionsstelle als Komplikation in wenigen Fällen hervorgehoben.

4 Fälle von generalisierten B.C.G. Prozessen, die alle tötlich verliefen, sind beschrieben worden.

4 Fälle wurden früher berichtet, in denen eine B.C.G. Ausbreitung auf dem Blutwege offenbar vorgelegen hat, wo es aber doch nur zur Entwicklung vereinzelter Herde von chirurgischer Tuberkulose kam.

Der Fall des Verfassers, ein Mädchen, wurde am linken Oberschenkel B.C.G. vakziniert als sie 3 Tage alt war und wurde im Alter von 4 Monaten revakziniert. Im Alter von 2½ Jahren fand man bei ihr eine Osteitis tuberculosa fistulosa tali sinistri. Man konnte bakteriologisch nachweisen, dass die Osteitis von B.C.G. verursacht worden war, die sich daher von der Vakzinationsstelle auf dem Blutwege ausgebreitet haben musste. Andere Herde fand man nicht. 4½ Jahre nach dem Erkrankungsbeginn wurde ein sowohl klinisch als auch röntgenologisch beinahe normaler Zustand gefunden.

Die Patientin war in adequater Weise mit einer Vakzine geimpft worden, die keinerlei Komplikationen bei den anderen Vakzinierten hervorrief. Die subkultivierten Bazillen zeigten eine für Meerschweinchen typische Virulenz.

Man fand niemals während des Krankenhausaufhaltes Zeichen für eine Herabsetzung der natürlichen Wiederstandsfähigkeit. Trotzdem kann man die Entwicklung einer progressiven Tuberkulose nur auf Grundlage eine herabgesetzten natürlichen Resistenz gegen B.C.G. erklären.

Die Patientin wurde in einer Altersperiode mit geringer Gammaglobulinproduktion vakziniert.

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