

MILKER'S NODULES WITH ALLERGIC SECONDARY ERUPTIONS

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Milkers and other persons who are in contact with cowpox-infected cattle sometimes catch the infection themselves. However, as recognized already by *Jenner* (1799), the cows may be infected either with "true" cowpox or with "false" cowpox. While true cowpox in human beings provokes vaccinia, false cowpox causes a disease known as "milker's nodules" (*Tuberculum mulgentium*).

It is supposed that milker's nodules are caused by a mutation of vaccina virus, or more probably by another related virus species, which *v. Pirquet* (1915) named *Paravaccine*. Smallpox vaccination does not give any protecting immunity against the paravaccine virus.

The clinical aspect of milker's nodules is very characteristic. After an incubation time of 7-10 days there appears in the skin a reddish papule which develops into a circumscribed, semiglobularly protruding, bluish red firm nodule, some 6-10 mm in diameter. Some days later the centre of the nodule, which can be somewhat umbilicated, appears more yellowish, and is surrounded by a livid and a grayish zone, while the edge of the nodule is of a livid red. The nodules can persist for many weeks and reach the size of 2 cm in diameter. In the end they subside spontaneously. The surface of the nodule may become ulcerated, with exudation and crust formation.

Histologically 4 stages can be distinguished. At first there is only an exudative inflammation in the papillary layer. In the second stage the epidermis of the young nodule shows a considerable acanthosis, with elongated delicate rete pegs, and with numerous mitotic figures in the basal layer. According to some observers, eosinophilic inclusion bodies may be present within the epidermal cells in early stages. Later, in the 3rd stage, a marked parakeratosis develops, and there is in the malpighian layer inter- and intracellular edema with multilocular vesicles and marked reticular degeneration.

In the corium there are at first no cellular infiltrates, only hyperemia and dilation of vessels. At a later stage, however, marked perivascular infiltrates occur, consisting of lymphocytes and histiocytes, intermixed with polymorphonuclear leukocytes. Eosinophils may be numerous, too, but plasma cells, epithelioid cells and giant cells are absent. There is a marked proliferation of capillaries, and the corium is thus site of a proliferative granulomatous process. The 4th stage is that of regression.

(For further histological details see *Gans; Pomus; Salkan; Schultze & al; Tiesenhausen; Woringer; Zurukzoglu & Kuske a. o.*).

Milker's nodules have frequently been described in the European dermatological literature, especially in the German, the largest case series having, however, been reported from Russia (*Dolgov & Morosov; Pomuss a. o.*). Probably they show an epidemic occurrence, being commoner than usual certain years. In USA they have up till now been considered very rare.

In some cases more acute *secondary eruptions* may occur as a complication (*Manke, 1898; Vollmer, 1906; Löhe, 1926; Schultze & v. Grundherr, 1929; Gottron, 1930; Steiner, 1931; Pomuss, 1934; Stark & al., 1934; Bonnevie, 1935; Katzenellenbogen, 1935; Zurhelle, 1936; Brants, 1939 a.o.*). These papulo-urticarial or erythema multiforme-like eruptions, often accompanied by swelling, appear about 6-17 days after the formation of the primary nodule. *Schultze & v. Grundherr* have considered them as toxic and as a parallel phenomenon to the postvaccinal exanthemas.

In opposition to the slowly developing and healing primary nodules, these secondary eruptions disappear, as a rule, within 1-2 weeks.

Bonnevie and others consider it as probable that these exanthemas are abortively developing secondary forms of mil-

ker's nodules, arising through lymphogenous (or more rarely through hematogenous) spreading from the primary lesion. Their abortive course is explained as being due to the allergic state caused by the infection.

Danbolt has recently (1949) described 3 cases of milker's nodules with complicating exanthema, observed in Norway. He holds the opinion that these exanthemas probably are allergic in origin.

While the primary lesion of milker's nodules has been described histologically by several authors, I have found only the following report concerning the microscopic picture of the secondary exanthema.

Schultze & v. Grundherr have described one case, consisting of 5 days old closely aggregated, firm, brownish red papular lesions, many of which showed a central umbilication. These lesions showed a thin and tense epidermis with flattened basal cells, which was separated from the underlying corium by multilocular subepidermal vesicles. These showed a fibrinous exudate, in some parts with numerous roundcells, in others with extravasation of erythrocytes. The epidermis remained in contact with the corium through the hair follicles and sweat ducts. Dilated blood vessels and numerous perivascular infiltrates were seen in the corium. The cells were—according to the authors—small roundcells of plasma cell type with well developed and intensively staining cytoplasm.

According to *Bonnevie* the secondary eruptions can occur in some epidemics more frequently than in others. This is perhaps also the case in the following four cases of milker's nodules that I observed in Finland in 1943 and 1944, all of which showed secondary eruptions. (cf. *Pomuss*: In a Russian series only 2 out of 81 showed a secondary exanthema).

CASE REPORTS

Case 1, maid on a farm, aged 18 (Seinäjäki).

Oct. 12, 1944 the patient noticed 3 nodular lesions situated on the medial aspect of the left little finger, on the dorsum of the left thumb and on the volar surface of the right ringfinger.

Oct. 16 the patient suddenly developed a *secondary* exanthema on both

forearms and upperarms, and, a little less intense, on the neck and in the sternal region. This secondary exanthema had, when first seen Oct. 17, the appearance of a contact dermatitis, with small papular or partly acneiform lesions, accompanied by redness and itching.

The original nodules showed, on Oct. 17, a partly ulcerated surface. The secondary exanthema was treated with shake lotion and was almost cured on Nov. 6. The nodules were still visible at this date, but in regression. They healed some weeks later.

Source of infection:

The patient had milked cows on a farm that had 8 cows. In the summer of 1944 one of the cows had showed a nodule on one of the dugs. A little later the patient had a similar nodular lesion on the medial side of the left leg, which healed in about a month. By the middle of September all 4 cows that she had milked showed lesions on their dugs, while 3 or 4 cows that had not been milked remained unattacked. The patient observed lesions on her fingers on Oct. 12, as mentioned above. Her employer, who had also milked the same cows, showed no lesions.

Case 2, farmer's wife, aged 42 (Ylistaro).

On Oct. 18, 1944, the patient developed a red nodular lesion, some 4 or 5 mm broad, on the dorsum of her right thumb (She thinks she may have had a tiny scratch in the skin). The nodule gradually grew and was considerably raised above the level of the surrounding skin. Some itching was present. Later the surface became ulcerated and oozing.

During the night of Oct. 30 a widespread *secondary exanthema* suddenly appeared on the backs of the hands on the forearms up to the elbows, as well as on both legs. This secondary exanthema was more pronounced on the extensor surfaces and seemed to be concentrated especially around the elbows and knee joints. A few lesions were seen on the nape of the neck also.

When first examined, on Nov. 1, the secondary exanthema displayed the symptoms of an acute papulo-urticarial or papulo-vesicular dermatitis, with deep lying, densely placed, tight vesicles of somewhat varying size (Fig. 1). There was also some redness and oedema of the cutis, and severe itching. On Nov. 2 the inflammatory symptoms had even increased, the hands, very swollen and red, were hot and stiff. The swelling subsided, however, in the course of 4-5 days by the application of compresses. After some 10 days (about Nov. 10) this exanthema had almost completely disappeared.

The allergic secondary eruption appeared now and again in December as a sudden onset of small groups of tiny, itching vesicles, which disappeared within a couple of days.

The solitary primary lesion on the thumb showed, on Nov. 1, a somewhat cockade-like appearance, the central nodule being surrounded by a wreath of small vesicles. The primary lesion remained for more than 4 months. By the



Fig. 1.

Case 2. Milker's nodule on the thumb, with papulo-vesicular secondary eruption (Nov. 1, 1944).

middle of February, however, it had subsided considerably, the redness began to disappear and only a flat papule was palpable.

Source of infection: The patient had milked cows since the summer. In the middle of September she got an evacuated cow (from Karelia) that was infected with numerous reddish nodules all over the dugs and on the udder. The eruption disappeared from this animal after a couple of weeks, about Oct. 1, and the cow was moved away. The patient had two cows of her own, in which the eruption did not appear until about Oct. 7. (The dugs of the younger cow were crowded with lesions, in the older one the lesions were fewer). On the patient the primary lesion appeared on Oct. 18. The patient had last been vaccinated against smallpox as a child.

Case 3, farmer's wife, aged 30 (Kauhajoki).

On Nov. 22, 1944 the patient noticed a papular lesion on the right thumb on the site of a scratch, and two days later a similar lesion on the left thumb and on the left index finger. At the beginning they were only 4-5 mm large but later they grew to pea-sized. They were firm, raised, bluish-red nodules, of an iris-like appearance, with a circular lighter ring between the centre and the periphery of the nodules. About Dec. 1, the surface became eroded.

On Dec. 8, a sudden onset of a *secondary exanthema* was noted on the hands and arms. On Dec. 10, the eruption spread to the legs. It was slightly itching and with small papular and papulo-urticarial or papulo-vesicular lesions raised above the skin surface. On Dec. 11 it was more marked on the extensor surfaces of the arms and legs than on the flexor side. Some rash was also present on the nape of the neck (Fig. 2). During the next two days the hands were markedly swollen, but the inflammatory symptoms disappeared

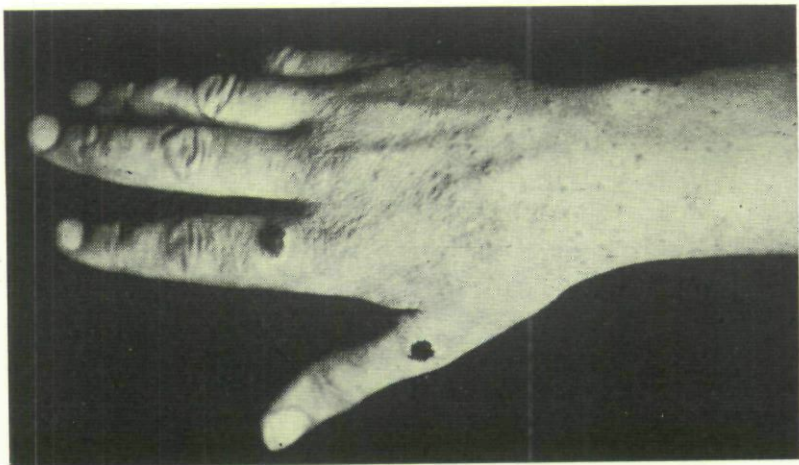


Fig. 2.

Case 3. Milker's nodules with secondary exanthema (Dec. 11, 1944).

within a few days after treatment with wet compresses. By the end of December the secondary exanthema was healed, and the nodular primary lesions covered by crusts. On Jan. 15 some livid discoloration and elevation on the sites of the primary nodules still remained—however healing.

Source of infection:

Nov. 1-Nov. 7, 1944 the patient had been milking two cows that showed a exanthema with numerous lesions on the dugs. (The patient's maid, who had milked the same cows in October, had had a slight exanthema on her hands).

Case 4, farmer's daughter, aged 21 (Suonenjoki).

Aug. 19, 1943 the patient noticed on her hands some red patches or flat papules, which gradually increased, reaching the size of peas and growing more protruding. Only slight itching or burning was noticed. The patient believes that all the lesions appeared almost simultaneously. When first examined on Aug. 25, the patient had a lesion on the back of the right hand, and one on the right hypothenar, and on the left hand one on the thenar and two on the dorsal side of the middle finger. All the lesions were of the same appearance: they were livid red, firm papules or nodules, standing out prominently from the skin surface and about 6 mm in diam. The centre was slightly umbilicated, showing a pale focus, surrounded by a bluish red ring. Outside this there was a pale ring, formed, as it were, by a dense row of micro-vesicles. This ring was, in its turn, surrounded by an intensely livid-red zone forming the periphery of the papule.

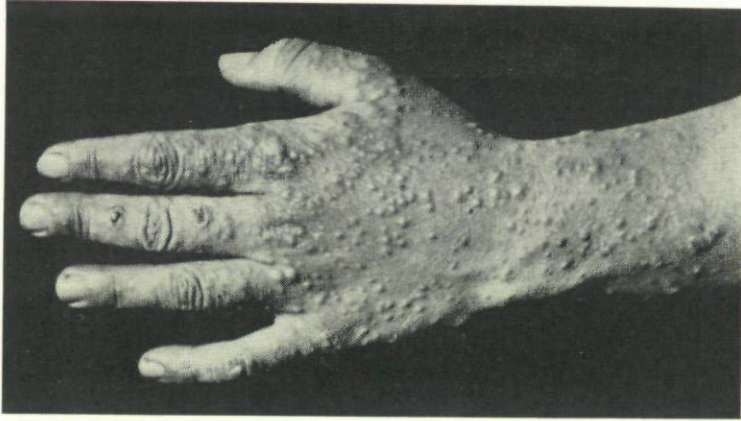


Fig. 3.

Case 4. Milker's nodules on the middle finger, with secondary exanthema.

Aug. 30 the lesions were up to 10-11 mm large, somewhat more umbilicated, and some of them with a small crust or a flat vesicle in the centre.

Sept. 7 the nodules showed regressive changes. The uppermost layer had been pushed off, exposing a fleshy red, clean, granulating surface, which still was raised above the level of the skin. However, two days earlier, on Sept. 5, the patient suddenly developed a widespread, itching *secondary eruption* on the backs of the hands, forearms and upperarms and on the legs. The exanthema was papulo-vesicular and reddish, somewhat reminiscent of erythema multiforme or of an epidermophytid. It consisted partly of point-shaped, partly of pinhead-to lentil-sized and strongly prominent lesions, and occurred on the extensor as well as on the flexor sides of the extremities (Fig. 3). The eruption also showed a *positive Köbner phenomenon*: A long excoriation from a twig that had scratched the left forearm formed a continuous row of papulo-vesicles.

Sept. 7 The exanthema had spread to the ears also.

Sept. 9 Exanthema somewhat better. Treatment with shake lotion. Biopsy.

Sept. 13 Considerably better, but the ears still oozing somewhat. WR-, Kahn-.

Sept. 20 Secondary exanthema subsiding. The patient was discharged Sept. 22, and Sept. 29 she was nearly cured.

Source of infection:

In the summer of 1943 the patient had milked cows that had crusted nodules on the dugs. The eruption disappeared from the cows also in September.

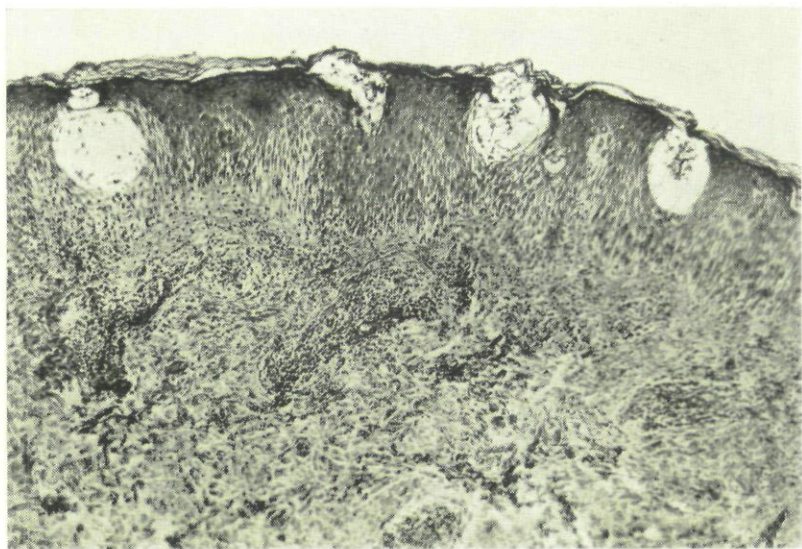


Fig. 4.
Case 4. Secondary exanthema (smaller lesion).

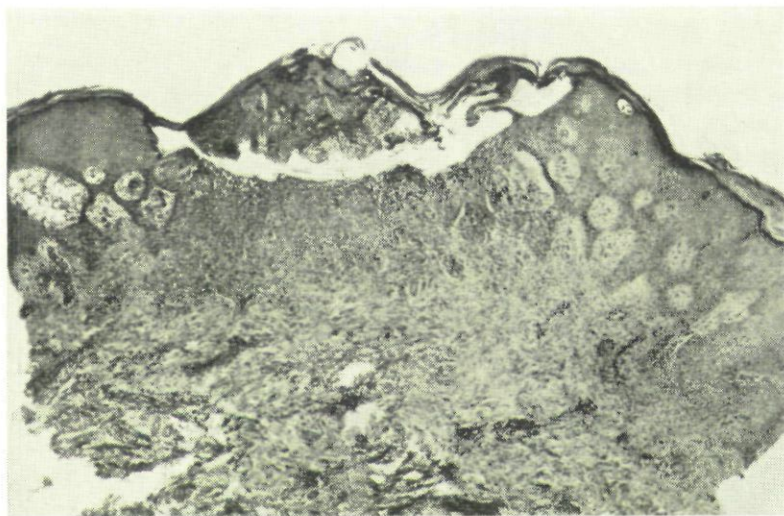


Fig. 5.
Case 4. Secondary exanthema (larger lesion).

COMMENT

The number of primary lesions in these four cases was 3, 1, 3 and 5, and the interval between the onset of the primary lesion to the onset of the secondary exanthema was 4, 12, 16 and 17 days, respectively. In the first case the sensitization time appears rather short. However, it is possible that the patient did not notice the indolent primary lesion from the very beginning.

Hands, fore-arms and upper-arms were involved in all 4 cases. Other locations were: legs in 3 cases, neck and sternal region (1 case), nape of the neck (2 cases) and in one case the ears. The exanthema was more pronounced on the extensor surfaces of the extremities, and in 2 cases a considerable swelling of hand-backs and fore-arms was observed. The exanthema consisted of papular and papulo-vesicular lesions, and itching occurred in all cases, being severe in one case. The exanthema subsided under treatment with indifferent compresses and shake lotions within about three weeks. In Case 2, which showed the severest reaction with considerable swelling, the exanthema disappeared almost completely within 10-11 days, but showed, a few weeks later, transient recurrences of small tiny itching vesicles, which disappeared within a couple of days.

A positive Köbner phenomenon was observed in Case 4. The patient showed a long continuous row of papulo-vesicles in the site of an excoriation(after a scratch from a twig).

HISTOLOGIC EXAMINATION

In one of the present cases (Case 4) the secondary exanthema was studied microscopically. Two papulo-vesicular lesions of different size were excised on the 4th day after the onset of the exanthema.

The smaller lesion (Fig. 4) shows an oedematous epidermis with marked spongiosis and vesicle-formation, but with

only very few migrating inflammatory cells. The horny layer is normal, the granular layer consists of a single row of cells, in some parts indistinct. The Malpighian cells are partly hydropic and in many areas widely separated from each other. Numerous unilocular and occasional multilocular vesicles are present, chiefly in the upper parts of the epidermis. Some of the vesicles are filled with exudate, in others a loose network of rounded epidermal cells is visible, intermixed with a few lymphocytes and polymorphonuclears.

The corium shows no oedema worth mentioning, but the endothelial cells of the vessel walls, appear swollen, and numerous perivascular infiltrates are present, consisting chiefly of lymphocytes. In the subpapillary region scattered and partly degenerated polymorphonuclear leukocytes are also observable. Plasma cells do not occur.

The larger lesion (Fig. 5) shows marked acanthosis and oedema of the epidermis. The horny layer is somewhat thickened, para-hyperkeratotic, the granular layer is thin and in the central parts absent. The Malpighian cells are hydropic, intercellular oedema with spongiosis and vesicle formation is also present. On the top of the lesion some epithelial necrosis and an intra-epidermal bulla formation is observable. In this part of the lesion numerous migrating lymphocytes and polymorphonuclears occur in the lower portion of the rete Malpighii. Rete pegs are lengthened and partly intercommunicating. The papillae are oedematous, showing enlarged and blood-filled capillaries. Enlarged vessels and some oedema is seen in the subpapillary region also. In the whole upper cutis scattered perivascular and perifollicular infiltrates are present, consisting predominantly of lymphocytes. In some cellular foci of the uppermost part of the corium polymorphonuclear leukocytes are numerous, the majority of them, however, degenerated.

There is endothelial swelling of capillaries and praecapillaries, and the vessel walls appear invaded by migrating round cells, chiefly lymphocytes. The epithelial cells of the

sweat glands are oedematously swollen, and a number of inflammatory cells can be seen around some of the sweat glands.

SUMMARY

Four cases of milker's nodules with secondary exanthema are described. It is felt that these exanthemas are allergic in origin. In one of the cases a positive Köbner phenomenon was observed. Microscopic examination of the secondary exanthema showed an eczematoïd reaction with spongiosis and vesicles in the epidermis, and inflammatory changes with oedema and perivascular (chiefly lymphocytic) infiltrates in the upper cutis. No plasma cells were seen.

ZUSAMMENFASSUNG

Es werden 4 Fälle von Melkerknoten mit Sekundärexanthem beschrieben. Das als allergisch aufgefasste Exanthem zeigte histologisch eine ekzematoïde Reaktion mit Spongiose und Vesikelbildung in Epidermis und mit perivaskulären, hauptsächlich lymphozytären Infiltraten in Corium. Keine Plasmazellen waren vorhanden.

Eines der Exantheme zeigte ein positives Köbner-Phänomen.

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