REVIEW ARTICLE

An Early Description of a "Human Mosaic" Involving the Skin: A Story from 1945

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In 1945, the *Journal of Heredity* published an impressive article entitled "A human mosaic: bilaterally asymmetrical noevus pigmentosus pilosus et molluscіformis unilateralis." The author was M. Zlotnikoff, a Russian physician working in Ivanovo, a city located approximately 250 km northeast of Moscow. Zlotnikoff described a 24-year-old woman with a congenital linear epidermal naevus in a systematized and strictly unilateral arrangement. For the first time, the author explained this disorder as a mosaic resulting from a somatic mutation that occurred at an early stage of embryonic development. However, because this article was published immediately after the war, it fell into oblivion, despite the fact that it was of utmost importance in clinical dermatology. Zlotnikoff's work is all the more remarkable as the author had never heard of the lines of Blaschko.

Key words: epidermal naevus; unilateral involvement; mosaicism; postzygotic mutation; lines of Blaschko.

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SIGNIFICANCE

In 1945, M. Zlotnikoff from Ivanovo, former Soviet Union, documented a unilateral systematized epidermal naevus in an adult woman. Without knowing about the lines of Blaschko, Zlotnikoff precisely described a Blaschko-linear cutaneous pattern. He explained this epidermal naevus as a biological mosaic resulting from an early postzygotic new mutation. However, because Zlotnikoff's manuscript was published immediately after the war, it remained unnoticed. During the second half of the past century, Blaschko's lines were "rediscovered" in dermatology. Today, it should be known that Zlotnikoff was an important forerunner in research on mosaicism and Blaschko's lines in human skin.

In 1945, an impressive article by a Russian author appeared in an American journal, the *Journal of Heredity* (1). It was presumably during the early 1940s that Zlotnikoff had submitted his manuscript to the journal. At the beginning of the report, an Editor's note states: "*This remarkable contribution came to hand some months before the war virtually suspended communications with the Soviet Union. Some suggestions for modifying the discussion of possible causes of the mosaic were addressed to the author and the manuscript was 'put on ice' to await his reply. In press of other matters it remained there much longer than originally intended. It may still be many months before we will hear from the author, so we are proceeding with the publication of the article essentially as submitted.*" Apparently, the Editor never heard from the author again.

The text of the Russian physician begins with the words: "The author has not been able to find a case of mosaic mutation in man in the available literature and therefore, he considers the present case to be worthy of publication. A careful study of the genealogy of this case showed that we may possibly deal with a case of a newly formed mosaic mutation."

ZLOTNIKOFF'S CASE REPORT

A 24-year-old woman, employed as an assistant veterinarian, presented to the Surgical Department of the 1st Medical Institute with a request to have "a pigmented patch" on the left side of her face and neck removed by surgery. Physical examination revealed several somewhat elevated patches forming a linear pattern beginning on the forehead and running to the cheek and neck. Moreover, the left side of her trunk showed similar lesions "going exactly down the midline of the body, from the forehead to the groin" (**Figs 1 and 2**). Her entire left leg was "of a dark brown colour as if it were covered by a stocking." Her scalp was bald on the left side (**Fig. 3**), and there was a difference in hair colour, "scarce light red on the right and abundant chestnut on the left." Fig. 3, however, clearly shows that the remaining scalp hair on the left side was partly depigmented. There was heterochromia iridum, grey on the left and dark brown on the right side. Tendon reflexes were of higher degree on the left side. X-rays did not reveal any pathological features.

At 158 cm the patient was below average height. She had been born as the seventh child in well-to-do peasant family. The skin lesions were present at birth. She began to speak rather late. When she was 2 or 3 years old, her parents noticed that her scalp hair was not uniform, being lighter and poorer on the left side.

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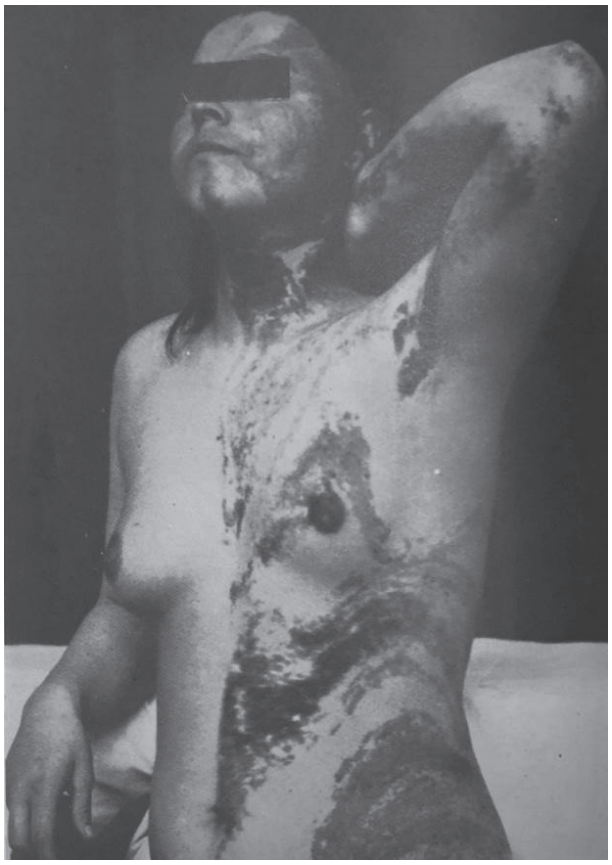

Fig. 1. A 24-year-old woman with systematized linear epidermal naevus, described by Zlotnikoff as "naevus pigmentosus pilosus et mollusciformis unilateralis", with a sharp separation down the midline (1). (Reproduced with permission from the American Genetic Association, USA, and Oxford University Press, UK).

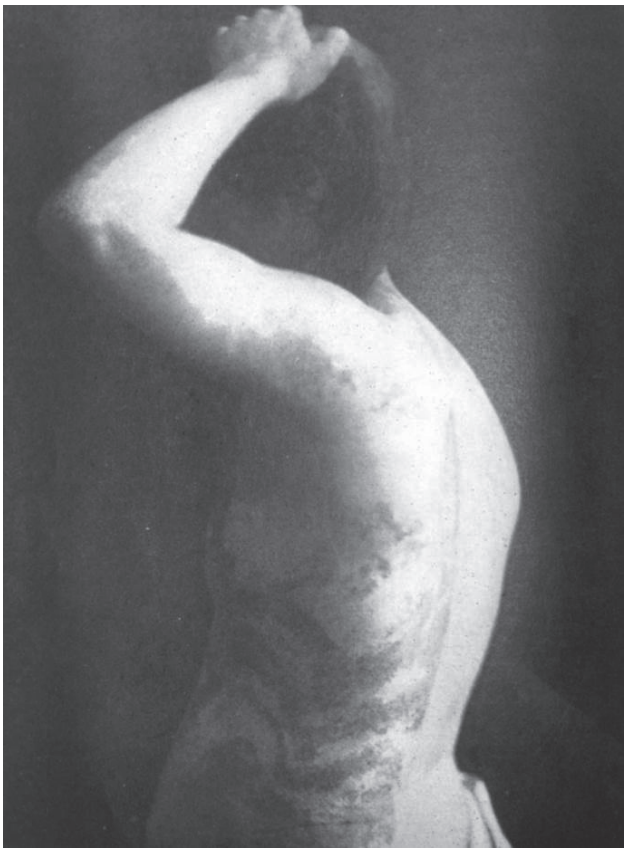

Fig. 2. The systematized linear lesions on the patient's back, likewise show an exact midline separation. (Reproduced with permission from the American Genetic Association, USA, and Oxford University Press, UK).

At 6 years of age, a large bald patch was strictly limited to the left side. Subsequently this hairless area extended to the neck and the frontal hairline.

The right half of her body was entirely normal. "The skin on the left side is partly of intense dark brown colour, partly crimson, and partly 'café-au-lait'."

On this side, "the pigmented regions form stripes like military 'shoulder-knots' from the shoulder to the spine." Ipsilaterally, "the upper abdomen is covered with a granular swelling of soft consistency, dark-red colour, slightly elevated in palpation. The colouration of the skin in this region reminds one of an oil-painting, where the paint has been applied in heavy 'dabs'. These have a semi-circular appearance, the rounded part directed upwards". There was no hair in the left axilla, whereas the right axilla showed abundant hair.

She reported that, since early childhood, whenever she made the slightest exertion, the left side of her body showed pronounced perspiration. The sweat stains were of dark-brown colour, being difficult to remove from the linen. On the right side sweating was normal.

As a child she was sometimes mocked as a "devil". During adolescence, the patient became morose and sullen and preferred solitude: "less mockery, less tears".

ZLOTNIKOFF'S EXPLANATION OF THE CONDITION

"If we assume that at the stage of two blastomeres a somatic mutation had taken place, i.e., one of these blastomeres underwent some mutation, then the development of these blastomeres would proceed in accordance with this mutation, i.e., the difference between the 'normal' and the mutated blastomere would exist in all stages of development of the organism. If we assume that in our case one of the blastomeres (at the two-blastomere stage) namely, the left underwent a mutation then we can easily understand from what has already been said that the left side of the organism would reflect all the features resulting from the mutation, that took place at the stage of the blastomeres, and the pathology of the organism would be strictly asymmetrical…. Assuming that this explanation is the most probable one, we are inclined to apply it in the present case, as it is impossible to give any other explanation to this one-sided asymmetry of mosaic mutation in our patient,…"

ZLOTNIKOFF'S FINISHING NOTES

At the end, the author makes the following touching remark: "The patient considers herself if not a blasto-

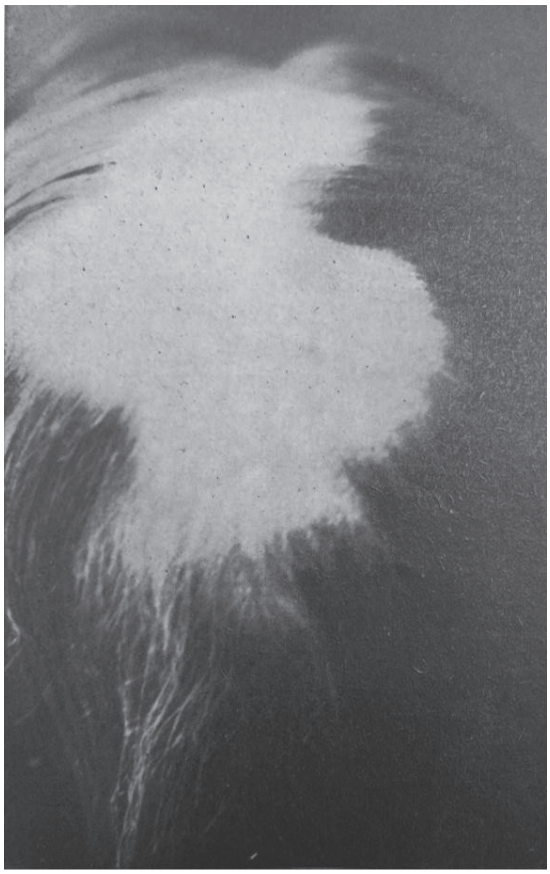

Fig. 3. Hair is lacking to the left of the midline, though part of the left side of the skull is unaffected. There is also a bald area above and back of the ear. (Reproduced with permission from the American Genetic Association, USA, and Oxford University Press, UK).

matous variation then a new species obtained as a result of a somatic mutation at the stage of two blastomeres."

In a last paragraph, Zlotnikoff mentions that "the patient was demonstrated at the Genetic Conference at the Institute of Medical Biology (director prof. Levit) in 1931 in Moscow."

HOW CAN WE CATEGORIZE THE EPIDERMAL NAEVUS IN THIS PATIENT?

The diagnosis is rather difficult. A sebaceous naevus is unlikely because of the presence of pronounced hyperhidrosis/chromhidrosis. Moreover, the bald area of the scalp is not suggestive of Schimmelpenning syndrome (2). Admittedly, lesional hyperhidrosis is a feature of phacomatosis pigmentokeratotica (PPK) that can today be taken as a particular variant of Schimmelpenning syndrome (3), but in the present historical case there was no papular naevus spilus that is known to be associated with hyperhidrosis (4). In oculoectodermal syndrome, an epidermal naevus can be associated with bald areas of the scalp and depigmented hair (5), but other features of Zlotnikoff's patient are not compatible with this diagnosis. In the present author's view, the phenotype described can best be categorized, at present, as an unclassifiable type of systematized epidermal naevus. However, this by no means interferes with the innovative significance of Zlotnikoff's report.

COMPARISON OF ZLOTNIKOFF'S EXPLANATION OF THE CASE WITH PRESENT KNOWLEDGE

At that time Zlotnikoff could not know that all human mosaics represent a mixture of normal and mutant cells (6, 7). The involved left half of his patient contained normal cells within the segmental areas of uninvolved skin as well as within the systematized epidermal nevus. Therefore, the assumption of a mutational event at the two-cell stage of embryonic development is too simplistic and cannot be upheld. In fact, segmental mosaicism tends to develop before the embedding of the fertilized egg into the uterine mucous surface, i.e., during the first week after fertilization (8). Hence, it is elusive to designate a "left" blastomere, as proposed by Zlotnikoff. Such minor historical imperfection, however, does not alter the remarkable fact that the author was on the right track in presenting a genetic theory to explain congenital linear skin lesions as a mosaic phenomenon.

SIGNIFICANCE OF ZLOTNIKOFF'S WORK

When submitting his manuscript, Zlotnikoff did not know about the ground-breaking publications of Alfred Blaschko on his "naevus lines" (9, 10). The intuition of the author from Ivanovo is even more stupendous when we read an additional note on his paper that appeared in the same issue of the *Journal of Heredity* (11). In this comment, the geneticist Bentley Glass from Baltimore, MD, USA, still expounded the then fashionable, but incorrect, theory of dermatomes: "A third interesting feature of the present case is the pattern of the markings, a pattern which strikingly suggests the dermatomes of the neurologists, especially those worked out of Head (12) on the basis of herpetic eruptions."

POLITICAL IMPLICATIONS OF ZLOTNIKOFF'S ARTICLE

In 1937, Stalin had announced, in a well-known speech, that those who still adhered to Mendelian genetics and the chromosome theory of heredity should be considered to be Trotskyist and revisionist enemies of the people. Thus, Stalin supported the charlatan Trofim Lysenko, who wanted to replace the "bourgeois" genetics of "Mendelism-Weismannism-Morganism" by his own absurd doctrine of inheritance of acquired characters (13). As a consequence, many geneticists lost their positions or were even executed. As a prominent example, the renowned Russian plant geneticist Nikolai I. Vavilov was sentenced to death in 1941 because he refused to renounce Mendelian genetics

and the genes as major factors of heredity. In 1943, Vavilov died of starvation in Saratov prison. To date, nothing is known about Zlotnikoff's fate, but we know that, in 1948, Lysenko managed to entirely eradicate scientific genetics in the Soviet Union: "Hail to the progressive Michurinian science! Glory to the great Stalin, the leader of the people and coryphaeus of progressive science!" (14). Hence, the question arises whether Zlotnikoff was aware of the fact that submitting his manuscript to an American journal was a very dangerous step.

CONCLUSION

As far as we know, M. Zlotnikoff was the first to explain the linear arrangement of a congenital human skin disorder by the concept of mosaicism, reflecting the action of a postzygotic mutation that occurred at an early developmental stage. This highly original idea was astounding, because the author had never heard of Alfred Blaschko's "naevus lines" (10). In 1976, Blaschko's work was "rediscovered" simultaneously and independently in Canada (15) and Germany (16). Robert Jackson from London, Ontario, Canada, discussed mosaicism as a possible mechanism, but concluded that "the embryological explanation on Blaschko's lines is not at all clear…I have been unable even to make a guess at what stage of development the changes occur which could provide a mechanism by which the localization of Blaschko's lines is determined. It would be helpful to tie in Blaschko's lines with some other dateable embryological event…" (15). Concurrently, such dateable event was proposed at a meeting in Heidelberg, Germany, in the form of X-inactivation (16, 17). This mechanism is known to occur at approximately day 5 after fertilization, prior to implantation of the blastocyst (18). By 1970, however, Widukind Lenz had already proposed to explain, without mentioning Blaschko's lines, the streaky pattern of incontinentia pigmenti by lyonization, and systematized epidermal naevi by early somatic mutations (18). Today, we can add M. Zlotnikoff's name to the group of authors who developed a genetic concept of how to explain Blaschko's lines. This early description of a human mosaic is all the more admirable because the author from Ivanovo did not know about Blaschko's work.

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