A NOTE ON THE OCCURRENCE OF HERPES ZOSTER IN HODGKIN'S DISEASE, LYMPHOSARCOMA, AND THE LEUKEMIAS

LLOYD F. CRAVER, M.D., AND CUSHMAN D. HAAGENSEN, M.D.
(From the Memorial Hospital, New York)

Herpes zoster is not uncommon in the generalized stage of cancer. German oncologists have pointed out, however, that this complication is much more frequent in lymphosarcoma, Hodgkin's disease, and the leukemias. The question has received scant attention in America. A series of seven cases observed at Memorial Hospital prompts this clinical review of the subject.

There are, apparently, various types of herpes zoster. The frequent and banal form is essential, idiopathic, or primary herpes zoster, which is an infectious disease accompanied by fever and leukocytosis. Its course is self-limited, and immunity results. It has been suggested that herpes zoster is related to other infectious diseases which are characterized by vesicular eruptions and which belong to the filtrable virus group. In a schematic arrangement of these diseases Rivers placed herpes zoster between varicella and symptomatic herpes. Attempts to cultivate the virus of herpes zoster have failed. Likewise, attempts to inoculate animals with the disease have failed in most hands. Cole and Kuttner have reviewed this phase of the subject, and have reported that they were unable to transmit the disease to rabbits, guinea-pigs, and monkeys, and to carry out cross-immunity tests. All aspects of primary herpes have been comprehensively reviewed by Doerr.

Secondary or symptomatic herpes zoster has been caused by a variety of processes. That appearing in the course of the common infectious diseases includes a large proportion of the cases. Varicella, pneumonia, influenza, diphtheria, meningitis, and pulmonary tuberculosis are the infections in which secondary herpes zoster most frequently develops. It was in connection with the latter disease that von Baren sprung, as early as 1863, presented the first pathologic proof that herpes zoster is due to changes in the spinal ganglia. The remarkable precision with which herpes zoster involved the area supplied by one or more spinal nerves, and its
unilateral distribution led him to the hypothesis that the spinal ganglia were responsible. At autopsy of a child dying of pulmonary tuberculosis shortly after an attack of thoracic herpes zoster, he found the spinal ganglia corresponding to the peripheral area involved to be grossly reddened and swollen. The inflammation extended for a short distance along the anterior and posterior branches but did not involve the nerve roots or the cord itself. Histologic study of the ganglia showed an inflammatory infiltration and the remains of blood pigment.

That there is a secondary type of herpes zoster caused by trauma or by pressure is proved by several pathologically controlled observations. Head and Campbell observed herpes zoster following an injury to the spine. Kamman noted thoracic herpes zoster produced by an intradural cyst.

Not infrequently herpes zoster has been observed following arsenic poisoning. One of the cases in which this correlation was most obvious was that reported by Jacob. Eighteen days after having ingested a considerable quantity of arsenic, and while symptoms of acute arsenical poisoning persisted, the patient developed extensive bilateral herpes zoster. That there is a toxic form of secondary herpes zoster, therefore, can hardly be doubted.

Considering the frequency of herpes zoster secondary to cancer, it is peculiar that there are not more of these cases on record. One of the earliest pathologic studies of herpes zoster, however, concerns this type. Charcot and Cotard reported a case of cervical herpes zoster developing from spinal metastases of mammary carcinoma. Cassière observed femoral herpes zoster in carcinoma of the cervix. Autopsy showed neuritis of the femoro-cutaneous nerve without carcinomatous infiltration.

Knowledge as to the pathogenesis of secondary herpes zoster has been derived very largely, however, from cases of lymphosarcoma, Hodgkin’s disease, and leukemia with this complication. The frequent association of herpes zoster with these diseases is probably due to the fact that they are particularly apt to involve the nervous system. Ginsburg has adequately reviewed the involvement of the nervous system in Hodgkin’s disease and has reported seven cases. Trömner and Wohlwill have made the most extensive study of involvement of the nervous system by leukemia, reporting twelve cases.

Head and Campbell, in their classical study thirty years ago, made the first pathologic investigation of the condition of the
spinal ganglia in herpes complicating this group of diseases. They reported one case of lymphosarcoma complicated by herpes zoster of the fourth dorsal area. At autopsy the upper seven spinal ganglia and posterior roots on the affected side were found to be surrounded by new growth. Of the spinal ganglia, only the fourth showed inflammatory and degenerative changes. Head and Campbell concluded that the herpes zoster was caused by the new growth surrounding and compressing the ganglion. Since Head’s and Campbell’s study, Fahr and Morton have each reported finding in cases of lymphosarcoma degenerative changes in the spinal ganglia corresponding to the peripheral area in which herpes zoster occurred. Freund and Fischl have each reported the same association in cases of leukemia.

In addition to the above reports of herpes zoster, in which the conclusions from autopsy are available, a considerable number of cases without pathologic study have been published. Burnam (two cases), Pancoast and Pendergrass (four cases), Ormsby, Schreus, and Andrews have reported herpes zoster complicating Hodgkin’s disease. Weber, Jadassohn (two cases), and Kreibich observed herpes zoster in the course of lymphatic leukemia. Tafie and Cassar, Carr, Schlesinger, and Ziel each reported a case in which herpes zoster developed during the course of myeloid leukemia. Halle has recently collected the reports of herpes zoster occurring in leukemia. He found sixteen such cases of lymphatic leukemia, five of myelogenous leukemia, and three of pseudo-leukemia—a proportion of three to one in favor of lymphatic leukemia. A noteworthy fact is that the localized herpes zoster was accompanied, or shortly followed, by a generalized vesicular skin eruption in 50 per cent of these cases. Jadassohn has devoted particular attention to this phenomenon. In his cases brownish papules developed after several weeks in the scars from the localized herpes zoster and also in the scars from the generalized eruption. Excision of these nodules showed them to be leukemic infiltrations.

The theory that lesions in the spinal ganglia are the cause of herpes zoster has recently been proved inadequate, however, by Wohlwill’s comprehensive pathologic studies of the disease. Wohlwill investigated the entire peripheral nervous system in six cases of idiopathic and four cases of secondary herpes zoster. (The primary diseases in the cases of secondary herpes zoster were gastric carcinoma, lymphosarcoma, lymphatic leukemia, and
He found that involvement of the spinal ganglia was not constant in either the idiopathic or the secondary type of herpes zoster. For instance, Wohlwill found the disease caused by carcinomatous infiltration of the anterior branch of an intercostal nerve, the dorsal ganglia remaining intact. In another case the posterior root was involved, and in another the posterior horn of the spinal cord, the dorsal ganglia being unaffected. These findings suggest to Wohlwill that herpes zoster can be produced by involvement of any point in the afferent portion of the reflex arc. It is true, however, that the dorsal ganglion is the most frequent point of involvement.

The question of the pathogenesis of herpes zoster has been further complicated by the findings in a subsequent study by Trömner and Wohlwill of the lesions in the nervous system in twelve cases of leukemia. They found frequent foci of leukemic infiltration in the dura, the epidural tissues, the cranial nerves, the spinal roots, and the gasserian ganglion. The gasserian ganglion was found to be involved in four of the nine cases in which it was investigated. None of these patients had had herpes zoster, however, despite the known involvement of the ganglion. Similar negative evidence is reported by Kirch. He described cases of neurofibromatosis in which tumors of one or more spinal ganglia, unaccompanied by herpes zoster, were found.

A number of years ago Cushing reported a case of secondary herpes zoster which cannot be explained by available theories of the pathogenesis of the disease. Following trigeminal neurectomy the patient developed a perineal herpes, which Cushing interpreted as representing a lesion of the fourth sacral posterior root ganglion. It is difficult to conceive the mechanism by which a posterior ganglion in the sacral region could be traumatized or infected in the course of a trigeminal neurectomy.

All this evidence suggests that the pathogenesis of herpes zoster is a highly complex and as yet unsolved problem. The very ubiquity of the disease is a great handicap to the theories which have been proposed. It is difficult to account for a manifestation which is secondary not only to most of the common infectious diseases, but also to trauma, to intoxication by poisons, and to the various neoplastic diseases, and which, in addition, occurs primarily as an infectious disease, sui generis, in otherwise normal individuals. It may well be asked whether all types of herpes zoster have a common etiology in a filtrable virus with which a large
proportion of the population is normally infected, and which is capable of producing local lesions in the afferent portion of the reflex arc in any region of the body which is the seat of a primary infectious or neoplastic disease or which has been traumatized or otherwise injured.

**MEMORIAL HOSPITAL DATA**

The 7 cases of secondary herpes zoster observed at the Memorial Hospital among 329 cases of lymphosarcoma, Hodgkin's disease, and leukemia were distributed as follows:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Cases</th>
<th>Number of Cases with Herpes Zoster</th>
<th>Percentage of Cases with Herpes Zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphosarcoma</td>
<td>59</td>
<td>3</td>
<td>7 per cent</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>72</td>
<td>3</td>
<td>4.5 &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td>Lymphatic leukemia</td>
<td>108</td>
<td>1</td>
<td>0.9 &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td>Myeloid leukemia</td>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The details of these cases follow:

**CASE 1**: E. O'C., an Irish postal clerk, aged fifty-seven. In March, 1929, he developed nodular swellings on each side of the neck and in the inguinal regions. At about the same time he had a severe attack of "bronchitis," with hemoptysis.

Examination in September 1929 showed several elastic, discrete, freely movable nodes in the upper cervical region on each side, and in the axillae and groins. The blood count was: R.B.C. 4,200,000; W.B.C. 12,600; polymorphonuclears 12; large lymphocytes 12; small lymphocytes 58; transitional cells 6; eosinophiles 2. A roentgenogram of the chest showed slight widening of the mediastinal shadow. One of the axillary nodes was removed and a histological diagnosis of lymphosarcoma was made.

The patient was given fractional exposures of high-voltage roentgen rays over the nodes, which decreased slightly in size under this therapy.

In March 1930, newly enlarged nodes were noted in the axillae and in both sides of the neck, and the spleen was felt 6 cm. below the costal margin. Coincident with these manifestations of renewed activity of the disease, a herpes zoster involving the segmental area of the 9th left dorsal nerve appeared (Figs. 1 and 2). The herpes zoster ran a normal course, lasting about three weeks. With further roentgen-ray treatment the new nodes decreased in size and the spleen became impalpable. The condition remained much the same in February 1931.

**Comment**: The appearance of the left-sided, lower dorsal herpes coincident with splenomegaly suggests that there was a correlation between the two phenomena.
Case 2: C. M., an Italian bricklayer, aged fifty-three. In October 1926, he first noted a small lump in the right axilla, which grew steadily in size. Supraclavicular nodes next became palpable, and finally inguinal nodes.

Examination in February 1927 showed a firm, fixed mass in the right axilla, 10 cm. in diameter. There were several enlarged firm nodes in each supraclavicular region and in each groin. The blood count was: R. B. C. 4,280,000; W. B. C. 7,400; polymorphonuclears 75; large lympho-
ocytes 8; small lymphocytes 14; transitional cells 2; eosinophiles 1. A roentgenogram of the chest was normal. A clinical diagnosis of lymphosarcoma was made.

Fractional doses of low-voltage roentgen ray were given over the masses of nodes, and within two months complete regression had occurred.

In June 1930 the patient developed a typical herpes zoster involving the segmental area of the 9th and 10th right dorsal nerves (Figs. 3 and 4). A roentgen examination of the spine showed no evidence of involvement. There was at the time no other manifestation of lymphosarcoma, no palpable nodes or enlarged visera. The herpes zoster ran a normal course. The patient remained without evidence of disease in February 1931.

Case 3: F. M., a Costa Rican machinist, aged thirty-one. In October 1923, he first had pain in the left chest, general enlargement of the neck, puffiness of the face, and general malaise. In March 1924, roentgenograms of the chest, according to his local physician, showed a tumor. Roentgen-ray treatments were given over a period of three weeks and his symptoms were promptly relieved. Early in 1926, however, his earlier symptoms returned.

On examination in June 1926, there was a mound-like protrusion of the chest wall along the right edge of the sternum from the first to the fourth interspace. Percussion and auscultation revealed an area extending from this mass laterally so as to obliterate the normal sounds over most of the upper two-thirds of the right lung. The blood count was: R. B. C. 4,320,000; W. B. C. 9,600; polymorphonuclears 67; large lymphocytes 6; small lymphocytes 20; transitional cells 5; eosinophiles 1. Roentgenograms of the chest showed a very large mediastinal tumor, extending particularly to the right. A clinical diagnosis of lymphosarcoma of the mediastinum was made.

During the following week the patient was given 30,000 millicurie hours with the emanation pack at 10 cm. over the right anterior mediastinum. His symptoms promptly disappeared, and when roentgenograms of the chest were taken two months later no evidence of the tumor remained. He continued well until September 1927, when he complained of distress in the upper abdomen after meals. A large smooth mass was then felt in the right upper abdomen. He was treated with fractional doses of low-voltage roentgen rays and within a month the abdominal mass could no longer be felt. In December 1927, however, a typical herpes zoster appeared in the segmental area of the right 10th dorsal nerve, and ran a normal course of about three weeks. This was the area in which the intra-abdominal tumor mass had but recently been treated.

In 1928 tumor masses appeared in the left supraclavicular region and the left upper quadrant of the abdomen and subsided under roentgen-ray treatment. In 1929 a mass the size of a grapefruit, which had appeared in the hypogastrrium, regressed with similar therapy. In 1930 a bulky irregular mass appeared in the right upper abdominal quadrant and disappeared promptly with only one fractional dose of high-voltage roentgen rays. Later in the same year a firm irregular mass, about 8 cm. in diameter, appeared deep in the pelvis in the region of the prostate. This also
disappeared after irradiation. Early in 1931 roentgenograms of the chest showed no evidence of disease.

Comment: This case illustrates the remarkable radiosensitivity of lymphosarcoma and the protean manifestations of the disease. The appearance of herpes zoster shortly after a tumor mass in the corresponding upper abdominal quadrant had regressed under radiation suggests that the tumor process in this region had extended to involve some part of the reflex arc.

Case 4: A. F., a Jewish school-boy, aged seventeen. About August 1928, he noted a lump in the left neck. A few months later nodes appeared in the right neck. He became pale, developed a slight cough, and lost his appetite.

Examination in March 1929 showed a thin, anemic boy with a large, firm, fixed mass of nodes at the base of the left neck. In the lower right neck there were a few small, discrete nodes. The area of mediastinal dullness was widened to the left. The blood count was: R. B. C. 3,600,000; W. B. C. 8,800; polymorphonuclears 75; small lymphocytes 12; large lymphocytes 8; transitional cells 2; eosinophiles 3. Roentgenograms of the chest showed a huge tumor lying in the anterior mediastinum, extending more to the left and capping the cardiac shadow. A clinical diagnosis of Hodgkin's disease with mediastinal involvement was made. A biopsy of one of the nodes in the neck showed Hodgkin's disease.

The patient was treated with fractions of high-voltage roentgen rays. His symptoms were partially relieved, and the mediastinal tumor and the cervical nodes diminished moderately in size within a month. The radiation was continued during the next few months with the result that the mediastinal tumor decreased somewhat more in size. In December 1929,
however, nausea and vomiting occurred. New nodes appeared in the upper cervical regions and in the occipital area. Coincidentally a typical herpes zoster involving the segmental area supplied by the 4th and 5th left dorsal nerves appeared (Figs. 5 and 6).

During 1930 the left ilium just above the acetabulum showed involvement. The spleen was 8 cm. below the costal margin. New nodes appeared in the axillae and groins. The areas of new growth slowly regressed under radiation.

Comment: This case, in which there was also a large mediastinal tumor, illustrates the lesser radiosensitivity of Hodgkin's disease as compared with lymphosarcoma. The occurrence of herpes zoster in the presence of a large mediastinal tumor which was most extensive on the same side suggests a correlation between the two processes.

CASE 5: T. G., an Irish factory worker, aged forty-eight. In the autumn of 1928 he noted a tumor in the right neck, which gradually grew larger. Similar masses appeared in the right axilla and left abdomen, and generalized pruritus, slight cough, and morning epistaxis developed.

On examination, in April 1929, masses of firm, freely movable nodes were present on each side of the neck and in the axillae. Those on the right were larger. The spleen extended 4 cm. below the costal margin. The blood count was: R. B. C. 3,712,000; W. B. C. 49,800; polymorphonuclears 78; large lymphocytes 2; small lymphocytes 20. Roentgenograms of the chest showed definite widening of the mediastinum. A biopsy confirmed the diagnosis of Hodgkin's disease.

Fractional doses of high-voltage roentgen rays gradually brought about relief from symptoms and almost complete regression of the nodes.
The spleen became softer to palpation but decreased only slightly in size. In September 1930, however, the nodes in the groins enlarged, the general condition failed somewhat, and a severe and extensive herpes zoster developed, involving the segmental area of the right 3rd and 4th cervical nerves (Figs. 7 and 8). It ran the usual course. In February 1931, following further radiation, the condition had changed but little.

Case 6: S. K., a Polish housewife, aged twenty-one. She had had amenorrhea for nine months, had lost ten pounds, and had observed nodes in the supraclavicular spaces and axillae for two months. A biopsy was done at another hospital and a diagnosis of Hodgkin's disease made.

When examined at the Memorial Hospital in October 1928, the patient had enlarged, firm, discrete nodes in each supraclavicular space and the left axilla. Her blood count was: R. B. C. 4,280,000; W. B. C. 10,200; polymorphonuclears 74; large lymphocytes 2; small lymphocytes 18; transitional cells 5. Roentgenograms of the chest showed moderate widening of the mediastinal shadow.

Fractional doses of high-voltage roentgen rays were given, and the nodes regressed markedly within eight days. The mediastinal widening decreased more slowly. In April 1929, the spleen and liver became enlarged, and cough and temperature up to 103° developed. Cervical, axillary, and inguinal nodes appeared. Further radiation controlled these symptoms only partially. In June 1929, involvement of the left ilium was noted. Chest roentgenograms showed extensive infiltration of both bases, presumably by Hodgkin's disease.

At this state of affairs, in November 1929, a typical herpes zoster affecting the left thigh in the segmental area of the 2nd and 3d lumbar nerves appeared. With further radiation general symptoms were somewhat improved. The patient has since been lost track of.

Comment: A herpes zoster appearing in the segmental area of the 2nd and 3rd lumbar nerves on the same side as coexistent involvement of the iliac bone suggests that there was extension of the disease to nearby nervous structures.

Case 7: W. S., a Russian clothes presser, aged forty-seven. During a period of a year he developed nodes in the left axilla, neck, and inguinal regions. These were treated with four roentgen-ray exposures. One of the nodes had been removed, and the histological picture was that of lymphatic leukemia. Within a week the patient had developed pruritus, a generalized skin eruption, and swelling about the eyes.

On examination at the Memorial Hospital in September 1928, there was a generalized papular skin eruption. Discrete, elastic nodes were felt in both sides of the neck, the axillae, and the groins. There was an upper abdominal mass, suggesting mesenteric adenopathy, and bilateral periorbital swelling. The blood count was: R. B. C. 4,136,000; W. B. C. 4,600; polymorphonuclears 6; large lymphocytes 90; transitional cells 4. Roentgenograms of the chest were negative. A diagnosis of aleukemic lymphatic leukemia was made.
Fractional doses of high-voltage roentgen rays brought about regression of the adenopathy and most of the symptoms. Anorexia, nausea, and occasional bleeding from the gums persisted. In October 1930 cervical and axillary adenopathy recurred, and a mass appeared in the left upper quadrant. These lesions regressed markedly with further radiation, but a month later a typical herpes zoster appeared in the segmental area of the left 11th dorsal nerve (Figs. 9 and 10). Roentgenograms of the spine showed no abnormality.

When the patient was last seen there was no change in his condition. The blood picture throughout the course of the disease has shown merely a change toward a more normal polymorphonuclear-lymphocyte ratio. A leukocytosis has not as yet appeared.

Comment: Here again we have a coincidence of a tumor mass in the left upper quadrant and a herpes zoster of the segmental area of the 11th dorsal nerve on the same side.

Discussion

A series of cases including autopsy study of the nervous structures probably involved would be more valuable than that reported herewith. On the basis of the clinical data it can be said only that these cases suggest that herpes zoster was due to the involvement of nervous structures by the tumor process. This relationship was most apparent in the four cases in which herpes zoster developed at or near the same time that a focus of the neoplastic disease appeared on the same side of the body and in the same general anatomical region.

Since there is no available statistical information as to the incidence of herpes zoster in the general population, it is impossible to give statistical proof that herpes zoster is abnormally frequent in the group of diseases under discussion. It can be said only that it is the writers' clinical impression that such is the case.
Summary

1. The development of herpes zoster should suggest to the clinician the possibility of an underlying lymphosarcoma, Hodgkin's disease, or leukemia.

2. The pathogenesis of secondary herpes zoster is not yet satisfactorily explained. Further pathologic studies of the extent of the involvement of the peripheral nervous system are needed.

Bibliography


Cassière: Zona fémorocutané dans un cas de cancer de l'utérus, Ann. de dermat. et syph. 6: 892, 1895.


