Experimental Studies on the Spread of Cancer in the Lymphatic System

III. Tumor Emboli in Thoracic Duct. The Pathogenesis of Virchow's Node*

IRVING ZEIDMAN

(Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia, Pa.)

The experiments here reported are part of a series on the lymphatic spread of cancer, investigated by a direct experimental method. In this method, living cancer cells are injected into the lymphatics (6, 7).

The present experiments were designed to ascertain what becomes of tumor cells injected into the thoracic duct: Are they all carried into the veins at the base of the neck, where the thoracic duct empties, and do they consequently form tumors in the lungs? Or do some of these cells pass directly from the thoracic duct into lymph nodes? These are questions of some importance in human cancer, and the answers may explain certain peculiarities of lymphatic metastasis, such as the occurrence of Virchow's node.

MATERIALS AND METHODS

The transplantable V2 carcinoma was used in domestic rabbits. Cell suspensions were prepared by pressing the tumor through a sieve into a mixture of balanced salt solution and rabbit serum. To determine whether tumor cells can pass from the thoracic duct directly to lymph nodes, 1.5 cc. of tumor suspension was injected into the thoracic duct via retroperitoneal lymphatics (Fig. 1). Each injection was made slowly, with a syringe and 27-gauge needle. Later, lymph nodes were examined microscopically for growing tumor. Other rabbits, serving as controls, received the same volume of tumor suspension intravenously. All rabbits were sacrificed 1–2 weeks after injection, and complete autopsies were performed. Numerous sections of the mediastinal and intercostal lymph nodes were studied microscopically. Tracheobronchial nodes were not included, as these would probably be the first sites of metastasis, were lung tumors to spread into the lymphatic system.

RESULTS

Of seven rabbits receiving thoracic duct injections, six developed tumors in mediastinal and intercostal nodes, and all seven revealed many pulmonary tumors. Other rabbits, used as controls, were given intravenous injections, and none of eight revealed tumor growth in mediastinal and intercostal nodes, although the lungs contained many tumors. Thus, tumor cell emboli in the thoracic duct pass not only into veins and thence to the lungs, but some go directly to nearby lymph nodes.

Location of the tumorous thoracic nodes.—The lymph nodes in which tumors were found were the superior mediastinal, above and at the level of the base of the heart, and the intercostal nodes (Figs. 2, 3). In three instances, a tumor growth was found anterior to the junction of the subclavian and common jugular veins, beneath the first rib on the left, but microscopic sections of these growths revealed no lymph node tissue (Fig. 4).

Absence of obstruction in the thoracic duct.—Passage of tumor cells from the thoracic duct to lymph nodes cannot be attributed to blockage of the thoracic duct. After the rabbits were sacrificed, dye injected into the thoracic duct outlined the duct to its termination and filled the left neck veins, showing that the duct was not obstructed.

Lymphatic connections of thoracic duct.—Once it was shown that tumor cells passed from thoracic duct to lymph nodes, it seemed desirable to visualize the channels permitting this passage. Dyes were used for this purpose. Berlin Blue or Mandarin Black was injected into thoracic ducts of fif-
The nature of the channels between the thoracic duct and lymph nodes.—What are these lymphatics through which tumor cells and dye pass so readily to nodes? Are they efferents, or is it possible that the thoracic duct gives off true afferents? This question can be answered by observing where in the nodes the tumor cells lodge and grow. As was previously reported, when afferent lymphatics were injected directly with tumor cells, early tumor growth was found invariably in and around the subcapsular sinus of recipient lymph nodes (6). Therefore, following injection of the thoracic duct, tumor growth in the region of the subcapsular sinus of nodes would indicate passage of tumor cell emboli through afferent lymphatics, whereas retrograde flow of emboli from duct to node would be indicated by early tumor growth in the medulla or hilus where the efferent lymphatic originates (2). In the above experiments 25 of 29 early tumor growths in lymph nodes were found in the region of the subcapsular sinus (Fig. 8). Only four growths appeared to be localized in the hilar region (Figs. 9, 10). Thus, the thoracic duct gives off true afferent branches to lymph nodes. Tumor cells usually pass from the thoracic duct to nodes through these afferents. Retrograde passage of tumor cells to nodes may occur infrequently.

Lymphatic connections of thoracic duct in the human.—A 5-month human fetus was given an injection of Berlin Blue via the thoracic duct to see if human ducts also branch to lymph nodes. Branches similar to those in rabbits were demonstrated (Fig. 5); mediastinal and intercostal lymph nodes were stained. In addition, left supraclavicular nodes were stained (Figs. 6, 7). This experiment, then, extends the observations on lymphatics between thoracic duct and lymph nodes to man. The channels in man communicate with the same nodes as in rabbits, and apparently with the supraclavicular nodes also.

DISCUSSION

In the light of these experiments, prevalent conceptions of the thoracic duct (1) and its anatomical connections and functions should be modified. Evidently, the duct does not empty exclusively into veins at the base of the neck, but also sends branches to thoracic lymph nodes. Part of the lymph in the duct passes through afferent lymphatics to these nodes, and returns to the duct through efferent branches. Part of the lymph in the duct is filtered by nearby nodes.

In man abdominal cancers often metastasize to lymph nodes of the mediastinum and to the supraclavicular node, especially on the left side ("Virchow's node," "Troisier's sign") (3–5). Hitherto, these metastatic cancers have been supposed to arise from secondary tumors in the lungs or from retrograde embolism from the thoracic duct aided perhaps by ductal obstruction (3, 5). Such explanations concerning the lymphatic spread of cancer have stemmed exclusively from morphological studies on autopsy cases. No experimental work has been reported previously. A simpler and different pathway is suggested by the present experiments. This explanation makes it unnecessary to assume spread of secondary lung tumors into the lymphatic system or blockage of the thoracic duct associated with retrograde lymphatic flow. Evidently cancer emboli may be carried directly from the thoracic duct through afferent lymphatic chan

FIG. 1.—Abdominal cavity of rabbit whose retroperitoneal lymphatics were injected with Mandarin Black. The retroperitoneal plexus is seen to the right of the fingers. Tumor suspension is injected at this site. These lymphatics lead directly to the cisterna clydi and thoracic duct. Also, no connections are found between the retroperitoneal lymphatics and substernal lymph nodes.

FIG. 2.—The posterior part of the right thoracic cage. The thoracic duct of this rabbit has been injected with dye. Lower arrow points to thoracic duct. Just above this arrow a small branch loops from the duct and apparently returns to the duct above. From the middle of this loop another larger branch (middle arrow) courses upward, bifurcates, and leads to stained superior mediastinal lymph nodes (upper arrow). The branching character of the thoracic duct is demonstrated.

FIG. 3.—Posterior part of thoracic cage of rabbit. The thoracic duct was injected with Mandarin Black. Lower arrow points to a looping branch originating from the thoracic duct; a stained intercostal lymph node is just above the loop. Middle arrow points to thoracic duct. Upper arrow points to stained superior mediastinal nodes. The branching character of the thoracic duct is demonstrated.

FIG. 4.—Section of tumor nodule found posterior to left first rib at its junction with sternum. This developed in three experiments following thoracic duct injection with V7 carcinoma cells. No lymph node tissue is found, so the original site of embolic arrest remains undetermined. Hematoxylin & eosin. ×140.
Figs. 5.—Posterior part of right thoracic cage of human fetus. The thoracic duct was injected with Berlin Blue. Lower arrow points to branching intercostal branch of thoracic duct. Note similarity of this branch to the intercostal branch in the rabbit of Figure 3. The loop crosses the inferior vena cava. Upper arrow points to injected thoracic duct.

Fig. 6.—Left supraclavicular region of human fetus. The thoracic duct was injected with Berlin Blue. The superficial neck muscles have been removed. Arrow points to dye-stained supraclavicular lymph node. This is a site where abdominal cancers often metastasize ("Troisier's sign," "Virchow's node"). Just below the node, the left clavicle appears as a pearly crescent.

Fig. 7.—Microscopic section of left supraclavicular node seen in Figure 6. The black amorphous material is the dye, Berlin Blue. The subcapsular sinuses on the right are almost completely filled with dye, suggesting arrival of dye via afferent lymphatics. Hematoxylin & eosin, ×75.
FIG. 8.—Section of superior mediastinal lymph node of rabbit. The thoracic duct was injected with \( V_2 \) carcinoma cells 8 days prior to sacrifice. Tumor is seen in and around region of subcapsular sinus, indicating arrival of tumor cell emboli via afferent lymphatics. Hematoxylin & eosin. \( \times 220 \).

FIG. 9.—Low-power view of section of intercostal lymph node. Rabbit was injected with \( V_2 \) carcinoma cells via thoracic duct 11 days prior to sacrifice. Arrow points to tumor-filled lymphatic in hilar region. Hematoxylin & eosin. \( \times 12 \).

FIG. 10.—High-power view of section in Figure 9, showing tumor growth in lymphatic of hilar region. Growth here indicates retrograde flow of tumor emboli from the thoracic duct to the lymph node through an efferent lymphatic of the node. Hematoxylin & eosin. \( \times 120 \).
channels to mediastinal, intercostal, and supraclavicular nodes.

SUMMARY

Experiments were performed to discover whether tumor cells in the thoracic duct are all carried to the lungs or whether some of them may go directly to thoracic lymph nodes. V_{2} carcinoma cells were injected in the thoracic duct of some rabbits and in a vein of others. In both series, tumors developed in the lungs. In animals receiving thoracic duct injections, tumors also developed in mediastinal and intercostal lymph nodes.

Lymphatic connections between the thoracic duct and lymph nodes were demonstrated by injecting dye into the duct. Some of these lymphatic channels are afferents, for tumor injection into the duct led to neoplastic growth in the subcapsular lymph sinuses of nodes, where afferent lymphatics empty. Only in a few instances was tumor found in the medulla or hilus, indicating retrograde passage through efferent branches. Thoracic duct branches were also demonstrated in a human fetus by dye injection. Mediastinal, intercostal, and left supraclavicular nodes were stained.

It is concluded that tumor cells may pass directly from the thoracic duct to nearby lymph nodes and there grow into secondary tumors without the necessity of passing through the lungs. Passage from the duct apparently occurs most frequently through afferent branches of the duct to the nodes. Virchow's node in man probably results from tumor cell emboli following a similar route to the supraclavicular nodes.

REFERENCES


Irving Zeidman


**Updated version**  Access the most recent version of this article at:  
http://cancerres.aacrjournals.org/content/15/11/719

**E-mail alerts**  Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.