Experimental Studies Bearing on the Question of Retrograde Spread of Hodgkin’s Disease via the Thoracic Duct

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SUMMARY

The simple purpose of this study was to determine by radiological and histological techniques whether lymph flow in an experimentally obstructed thoracic duct is reversed and whether particulate or fat-soluble radiopaque contrast material placed directly into the lumen of the obstructed duct in dogs is carried retrograde to nodes below the diaphragm. In 15 of 16 dogs in which contrast material was so placed as to lie entirely within the intrathoracic portion of the ligated duct, there was no subsequent movement to nodes below the diaphragm. In contrast, in six other dogs in which contrast material was placed so that its lower level extended initially to the cisterna chyli just below the diaphragm, the material was subsequently demonstrable in lower paraaortic and/or presacral nodes and histologically was located predominantly in the subcapsular sinus and peripheral cortex. These findings bear directly on the question of whether Hodgkin’s disease spreads from the neck to the abdomen due to reversal of flow in a thoracic duct obstructed by enlarged supravacuolar nodes. As results indicate that flow in the intrathoracic portion of the obstructed duct is usually not reversed, retrograde dissemination via the thoracic duct seems unlikely. On the other hand, retrograde lymphatic dissemination to paraaortic and presacral nodes from an infradiaphragmatic focus near the cisterna chyli is clearly possible when thoracic duct flow is impaired.

INTRODUCTION

Almost all knowledge of Hodgkin’s disease has been acquired by analysis of clinical data; in general, it has not been possible to answer questions about the disease by recourse to experimental studies in animals. Whether the disease spreads retrograde from the neck to the abdomen as a result of reversal of flow in a thoracic duct obstructed by enlarged supravacuolar lymph nodes remains a particularly urgent question and an unusual one, in that it should lend itself to such an approach. An attempt to unravel this problem by determining the direction of lymph flow following experimental ligation of the thoracic duct in dogs forms the basis for this report.

To support the view that the disease spreads retrograde from the neck to the abdomen, Kaplan (8), one of the leading proponents of the theory, recently cited results of radiographic studies in experimental animals by Neyazaki et al. (10). The latter workers injected radiopaque contrast material into lymphatic vessels in the lower extremities of dogs undergoing experimental obstruction of the thoracic duct and noted reflux of contrast material into abdominal tributary vessels. Similar findings have been described by others (7). All such studies have in common the injection of contrast material into lymphatics of the lower extremity. To consider that reflux developing under such circumstances is evidence for retrograde flow from the upper portion of the duct backwards to the cisterna chyli is to ignore backflow that develops from dilated infradiaphragmatic channels that are directly in line with vessels injected. Based on these considerations, direction of flow in the obstructed thoracic duct was studied in experimental animals by ligating the duct in the midportion of the right chest, placing small amounts of radiopaque contrast materials directly into its lumen just below the point of obstruction, and then following lymphatic distribution of these materials by radiological and histological techniques.

MATERIALS AND METHODS

Studies were performed in 22 adult mongrel dogs (10 to 15 kg body weight). Under i.v. Pentothal anesthesia and by means of aseptic techniques, the thoracic duct was approached through a right thoracotomy incision through the 6th intercostal space and was ligated at the level of the 5th or 6th thoracic vertebra. Particular attention was directed to the identification and ligation of any additional parallel ducts to ensure that obstruction was complete. Immediately following ligation in some dogs and, in others (by means of a 2nd thoracotomy), after an interval of 1, 2, 3, or 4 weeks, the duct was cannulated in a retrograde direction just below the ligature and either Ethiodol (10 dogs) or a suspension of tantalum particles (12 dogs) was injected into the lumen. Pressure and volume of injection were carefully controlled so that the contrast materials (0.1 to 0.3 ml) were confined to the intrathoracic portion of the duct in 16 dogs, designated Group 1. In the remaining 6 (Group 2), slightly more contrast material was injected (0.4 to 0.7 ml) so that the lower limit of duct opacification extended just below the diaphragm. Immediately following injection, the cannula was removed and 2 ligatures previously placed around the duct were tied to prevent escape of contrast material. Radiographs were obtained immediately after injection, at

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24 hr, and later at intervals that ranged from several days to 1 week, for a total period of 6 weeks from the time of injection. At the end of this time, the animals were sacrificed and the thoracic duct was examined to confirm the persistence and completeness of obstruction. At the same time, lymph nodes in the neck, chest, and abdomen were examined grossly and then were removed, together with samples of liver and spleen, for radiographic and histological studies.

When tantalum particles (average size, 1 to 2.5 µm) were used as the radiopaque contrast material (Pfansteel Corp., Chicago, Ill.), fresh suspensions were prepared for each experiment as follows: 100 ml of 10% sorbitol were added to 25 g of tantalum powder and stirred for 1 hr in a VirTis homogenizer (2).

RESULTS

Results of radiographic and histological studies are summarized in Table 1.

Radiographic Studies. In 15 of 16 dogs in which contrast material initially filled only the intrathoracic portion of the duct, there was no subsequent retrograde movement of this material to lymph nodes below the diaphragm (Figs. 1 and 2). In the 1 exception, a dog that received Ethiodol 2.5 weeks after duct ligation, paraortic glands were noted to be radiopaque 24 hr later. In all 6 animals in which sufficient contrast material was injected to immediately opacify the thoracic duct, down to and including the cisterna chyli below the diaphragm, subsequent radiographs disclosed retrograde transport of the infradiaphragmatic portion of the material to lower paraortic and/or presacral lymph nodes (Figs. 3 and 4). Opacification was first noted in these nodes 1 to 4 days following injection, and this usually became less prominent by the time the animals were sacrificed on the 40th to 42nd day. Radiographic evidence of antegrade flow around the obstruction was noted in some animals in both groups beginning 24 hr after injection, and this consisted of opacification of collateral lymph vessels or nodes at and above the point of ligation. Radiopacification of liver and spleen was not observed. There were no radiological differences between the distribution of Ethiodol and that of tantalum, although the latter provided better delineation of lymph nodes.

Gross and Histological Observations. At the time of sacrifice, the thoracic ducts were found to be completely obstructed in each dog. When the duct was opened below the ligature, lymph escaped under pressure and, in the case of animals receiving tantalum, the escaping fluid was dark gray. In animals in which the injected tantalum initially extended to the cisterna chyli below the diaphragm, one or more lower paraortic or presacral nodes were also distinctly gray-black.

Fine gray-black lymph vessels could be seen in most animals in both groups, extending from the duct below the obstruction laterally along intercostal vessels. In addition, in some animals a cervical node was found similarly discolored by tantalum.

Histological studies confirmed both radiographic and

<table>
<thead>
<tr>
<th>Dog</th>
<th>Contrast material</th>
<th>Interval between obstruction and injection (days)</th>
<th>Extent of initial thoracic duct opacification</th>
<th>Radiopacification of nodes BD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Histology of nodes BD</th>
<th>Additional histological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>436</td>
<td>Tantalum</td>
<td>0</td>
<td>BD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Tantalum in retrosternal and cervical nodes</td>
</tr>
<tr>
<td>441</td>
<td>Ethiodol</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Tantalum in spleen</td>
</tr>
<tr>
<td>443</td>
<td>Tantalum</td>
<td>24</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Tantalum in intercostal node</td>
</tr>
<tr>
<td>445</td>
<td>Tantalum</td>
<td>14</td>
<td>BD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Tantalum in lung</td>
</tr>
<tr>
<td>446</td>
<td>Ethiodol</td>
<td>17</td>
<td>AD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Tantalum in intercostal node, lung, and spleen</td>
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<tr>
<td>447</td>
<td>Tantalum</td>
<td>7</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Tantalum in retrosternal node</td>
</tr>
<tr>
<td>450</td>
<td>Tantalum</td>
<td>7</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>457</td>
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<td>Pos.</td>
<td>Pos.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
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<td>AD</td>
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<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>459</td>
<td>Ethiodol</td>
<td>14</td>
<td>BD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>464</td>
<td>Tantalum</td>
<td>14</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>465</td>
<td>Ethiodol</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>467</td>
<td>Tantalum</td>
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<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>470</td>
<td>Tantalum</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Tantalum in spleen and lung</td>
</tr>
<tr>
<td>471</td>
<td>Ethiodol</td>
<td>0</td>
<td>BD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>472</td>
<td>Ethiodol</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>473</td>
<td>Ethiodol</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>474</td>
<td>Tantalum</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>475</td>
<td>Tantalum</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>477</td>
<td>Tantalum</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>478</td>
<td>Tantalum</td>
<td>0</td>
<td>AD</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Ethiodol in retrosternal node</td>
</tr>
<tr>
<td>480</td>
<td>Tantalum</td>
<td>0</td>
<td>BD</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Tantalum in hepatic node</td>
</tr>
</tbody>
</table>

<sup>a</sup> BD, below the diaphragm; AD, above the diaphragm; Pos., positive; Neg., negative.
gross observations. In 15 of the 16 dogs in which injected contrast material was confined to the intrathoracic portion of the duct, it was absent histologically in sections of abdominal nodes. Contrasting findings were noted in the 6 dogs in which contrast material initially extended below the diaphragm. In every one of these animals, in which radiopacification of lymph nodes was also noted, contrast material was found in the node histologically. These findings were particularly striking in the 3 animals in which tantalum was used as the contrast material, but a residue of Ethiodol was also demonstrable in the 3 others. The injected material was found in either a paraaortic or presacral gland, or both, and this deposition predominated in the region of the subcapsular and/or peripheral cortex (Fig. 5). Sections of cervical and upper mediastinal lymph nodes of dogs in both groups also contained tantalum particles at times but in amounts that were apparently too small to render them radiopaque. Here too, deposition of particles predominated in the subcapsular sinus and peripheral cortex. Although radiopacification of the spleen was never observed, histological examination disclosed tantalum particles in 3 dogs of Group 1.

DISCUSSION

Specific clinical or experimental data indicating that thoracic duct obstruction leads to retrograde flow of lymph from the upper portion of the duct to nodes below the diaphragm are completely lacking. The results here, in which such a pattern was observed only once in 16 consecutive experiments, indicate that this occurs rarely.

The incidence of complete obstruction to lymph flow in either the cervical or thoracic portion of the duct in patients with Hodgkin's disease is unknown, but information available from lymphangiographic studies suggests that it occurs infrequently (1, 11). The fact that cannulation of the thoracic duct in patients regularly yields a free flow of lymph regardless of the so-called "stage" of the disease appears to conform with this view (4, 5). On the other hand, should some impairment of thoracic duct flow develop (and incomplete obstruction might not be recognizable either on lymphangiograph or thoracic duct cannulation), the results suggest that retrograde lymphatic dissemination from an infradiaphragmatic focus near the cisterna chyli is likely. In this event, dissemination is apt to be via collateral channels that rejoin afferent lymph vessels enroute to paraaortic and presacral nodes and not by simple backflow through obstructed efferent vessels. This view is based on the histological demonstration of contrast materials in the subcapsular sinus and peripheral cortex of these nodes, a distribution signifying transport to nodes via afferent lymphatics (17).

Lymph vessels arise from veins, and mediastinal communications between these structures persist and become functional when flow in the thoracic duct is impaired (3). Lymph flow through such shunts probably explains movement of tantalum particles from an obstructed thoracic duct into the systemic circulation with eventual sequestration in spleen. It is also recognized that ligation of the thoracic duct in the neck or chest is not followed by any permanent sequelae. In humans as well as in experimental animals, antegrade flow is maintained via collateral channels and lymphatic-venous shunts (9, 14, 15). The demonstration of contrast material in cervical and mediastinal nodes above the point of obstruction and in the spleen in the studies reported here conforms to this view.

While the sequence and mechanism of nodal involvement in Hodgkin's disease are still unknown, a number of clinical observations are not inconsistent with the view that the disease spreads by retrograde extension via the thoracic duct from the neck to the abdomen. To state however that "Extension from the lymph nodes at the base of the neck by way of the thoracic duct to the upper lumbar paraaortic lymph nodes is a major escape route for the disease" (8) is to imply the presence of specific information which is, in fact, lacking. Actually such a mode of spread would be unusual in other neoplastic and/or infectious disorders and experimentally appears incapable of duplication. Other explanations must be sought to explain observations such as those reported by Glatstein et al. (6) "of well documented instances of development of Hodgkin's Disease in the paraaortic lymph nodes at intervals of 2-4 years or more following radiation therapy to disease clinically limited to the neck." The latter could result from impairment to antegrade thoracic duct lymph flow with retrograde spread from clinically unrecognized foci in upper abdominal lymph nodes. Hepatic hilar lymph nodes, for example, are never opacified with conventional lymphangiography and are usually either overlooked or considered inaccessible during laparotomy for staging. Moreover, a possibility that the disease spreads initially in an antegrade direction from such a site via the thoracic duct to the neck would not be incompatible with either clinical or experimental observations (12, 13, 16).

REFERENCES

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Fig. 1. Dog 478. Radiographs taken 3 hr, 24 hr, and 6 weeks (left to right) after tantalum was injected directly into the obstructed thoracic duct. No opacification of abdominal lymph nodes is seen here or on other radiographs taken at weekly intervals up to 6 weeks.
Fig. 2. Dog 472. Same experiment and result as in Fig. 1, except that Ethiodol was used as contrast material.
Fig. 3. Dog 480. Radiographs taken 3 hr (left) and 6 days (right) after tantalum was injected directly into the obstructed thoracic duct. The volume of injection was large enough to opacify the duct from the point of injection to the cisterna chyli below the diaphragm. Radiograph at 6 days shows tantalum in abdominal lymph nodes (arrows).
Fig. 4. Dog 471. Same experiment and result as in Fig. 3, except that Ethiodol was used as contrast material.
Fig. 5. Dog 445. Histological sections of paraortic lymph node showing tantalum particles in subcapsular sinus (left) and peripheral cortex (right). H & E, × 150.
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