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Lymphographic Visualization of Lymphaticovenous Communications and their Significance in Malignant Hemolymphopathies

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The presence of lymphaticovenous communications (l.v.c.) besides the junction between the thoracic duct and the left subclavian vein is no longer doubted today. Experimental studies (2, 3) as well as the anatomical dissection studies (10, 14) have proved the existence of such communications at all levels. Lymphography has made them visible in vivo. Their visualization is always related to an obstruction of the lymphatic flow, due either to node metastases (1, 7, 8, 9, 16, 17) or to sclerosis subsequent to x-ray therapy (5), as well as to surgical interruption of lymphatic circulation after removal of lymph nodes (1, 12). Only few papers mention l.v.c. in malignant hemolymphopathies (5, 6, 11, 13).

It appears that in humans l.v.c. begin to function only in pathologic conditions i.e. in case of defficiency of the lymphatic chains which become inadequate to prevent the

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accumulation of lymph in the interstitial or free spaces of the organism. On the other hand the opening of l.v.c. might favour the spread of tumor cells in the blood circulation and the occurrence of distant metastases.

The object of this paper is to demonstrate by radiographic examination the presence of l.v.c. and to discuss the significance the opening of these communications might have in the evolution of some malignant hemolymphopathies.

Material and Methods

We have studied lymphographies from patients who have been subjected since 1966 to careful radiologic investigation of the disturbances of lymphatic flow. Finally we have chosen the patients with malignant hemolymphopathies (122 cases). All these patients have been subjected to detailed clinical and biologic examinations and have been classified according to the clinical stage prior to/and after lymphography. Particular emphasis was laid on the first lymph node involvement, on the site of subsequent adenopathies and on the previous treatments with special reference to the consequences the presence of l.v.c. might have in the evolution of disease.

Lymphography was performed according to Kinmonth' classic method by bilateral intra-lymphatic injection of 8–10 ml. Ultrafluid Lipiodol *(Guerbet)* in each limb. Injection was made at a constant pressure by means of a device which has been developed in our Institute. The device is based on the principle of simultaneous injection of contrast medium by means of two independent 10 ml syringes operated by a motor system with adjustable speed (11).

We have chosen a slow rate of injection – 1 ml in 8–10 minutes – to avoid extravasations and as much as possible pulmonary accidents. Injection was carried out under lymphangiographic monitoring for a better overall view of the lymphatic vascularisation and to enable a better differentiation between the lymphatic and the venous vessels.

The first radiograph was obtained after injection of 1 ml. Ultrafluid Lipiodol (U.L.) and then the lymph flow was followed up on serial x-rays after every 2,5 ml of injected contrast medium.

Injection of contrast medium was not stopped even in patients in whom l.v.c. were demonstrated. The radiographic aspect of U.L. penetration into the venous blood is rather characteristic: small clusters of round droplets. But owing to the rapid blood flow the picture is transient and may be missed on inadequate radiographic examination. Therefore as soon as a disturbance of lymph circulation appeared the progress of contrast medium was more thoroughly followed up by rapidly developed films after every 1 ml of injected contrast material. At the end of the first day examination we obtained a thoracic film. After 24 and 48 hrs., beside x-ray examinations of the node groups a chest roentgenogram was again obtained. If necessary the patients were further radiographically controlled.

Results

The results of these investigations are presented in tables 1 and 2. In the total group of 122 patients with malignant hemolymphopathies the lymphographic examination detected 8 patients with l.v.c. namely: 6 out of 63 with Hodgkin's disease and 2 out

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of 12 with reticulum cell sarcoma. No patient with chronic lymphocytic leukemia or lymphosarcoma (42 patients in all) had such anastomoses. Therefore the frequency of l.v.c. in the diseases of the same nosologic group varies and seems to be more frequent in Hodgkin's disease and in reticulum cell sarcomas. Our observations are in agreement – from this point of view – with those in the literature in which only one case of lymphosarcoma with l.v.c. is reported (16).

Table 1 Frequency of lymphatico-venous communications according to diseases.

Disease	Number of cases investigated	Number of cases with lymphatico-venous communications	Frequence %
Hodgkin	63	6	9,7
Lymphosarcomas	30	0	0
Reticulum cell sarcomas	12	2	17
Chronic lymphocytic leukemias	12	0	0
Malignant reticuloses	5	0	0
Total	122	8	6,6

L.v.c. were detected in various periods of evolution of the disease. Table 2 shows the cases with only 2 or 3 nodes involved and classified at stage II prior to lymphography, the cases 3, 4, 6, and 8 in which l.v.c. occurred shortly after onset of disease. In cases 1, 2, 5, and 7 of the same table they occurred in stages III and IV. In all these patients there was a blockage of lymph circulation caused by more or less voluminous adenopathy.

Table 2 Survival time of patients calculated since onset of disease and since detection of lymphatico-venous communications according to clinical stage and condition of lymphatics.

No.	Name	First nodal localization	Histopathologic type of lymphoma	Clinical stage prior to lymphography	Condition of lymphatics	Survival time (months) Since onset	Since lymphographyc l.v.c.
1.	B. Z.	Mediastinal	Hodgkin	St. III A	few collaterals	60	11
2.	B. I.	Inguinal	Hodgkin	St. IV	multiple collaterals	144	10
3.	S. Ch.	Inguinal	Hodgkin	St. II B	absence of collaterals	8	6
4.	S. M.	Supraclavicular	Reticulum cell sarcoma	St. II B	few collaterals	14	6
5.	E. C.	Inguinal	Reticulum cell sarcoma	St. III B	absence of collaterals	16	8
6.	N. I.	Inguinal	Hodgkin	St. II B	few collaterals	24	14*
7.	C. M.	Supraclavicular	Hodgkin	St. III A	absence of collaterals	11	7*
8.	D. A.	Supraclavicular	Hodgkin	St. II A	absence of collaterals	35	26

* Alife at the present time.

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The presence of l.v.c. in a particular site is always related to that of adenopathy in the immediate vicinity whose damaged nodes are generally enlarged and have a completely changed architectural pattern (fig. 1). In some cases there is even absence of nodal opacification (fig. 2 a and 2 b).

The site of l.v.c., usually proximal to adenopathies has been in 7 cases in the pelvis (fig. 1, 3, 4, 5, 6) and only in one case in the paralumbar region (fig. 2 a).

Beside the relationship between the location of l.v.c. and that of adenopathies, we have observed – among the cases studied by us – a fairly close relationship between the frequency of l.v.c. and the nodal onset of disease. It seems that in patients with

Fig. 1 B. Z. Hodgkin's disease, stage III A. Right unilateral lymphography. Diffuse enlargement of right external iliac node. L.v.c. visualized during the injection (arrows).

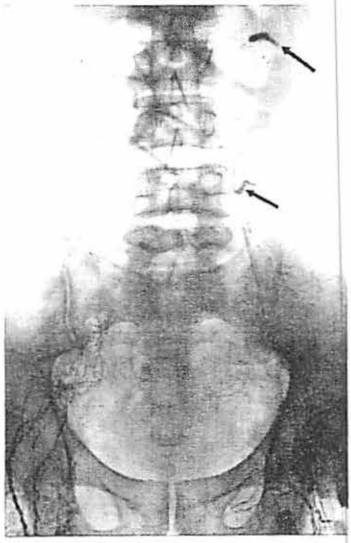

Fig. 2a

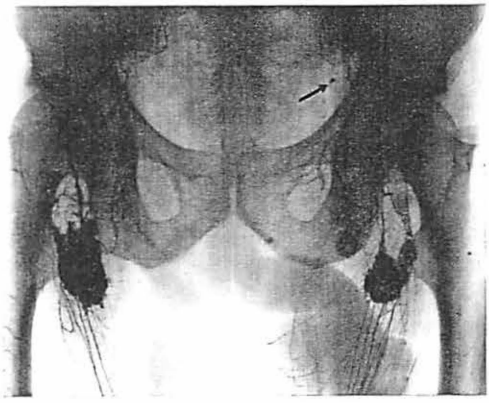

Fig. 2b

Fig. 2a and 2b B. I. Hodgkin's disease. Stage IV prior and after lymphography. Films taken at the end of injection. Almost all the nodes replaced. Numerous lymphatic collaterals and lymphatic intercommunications in the pelvis and dermal back-flow. L.v.c. in the left para-aortic region (arrows).

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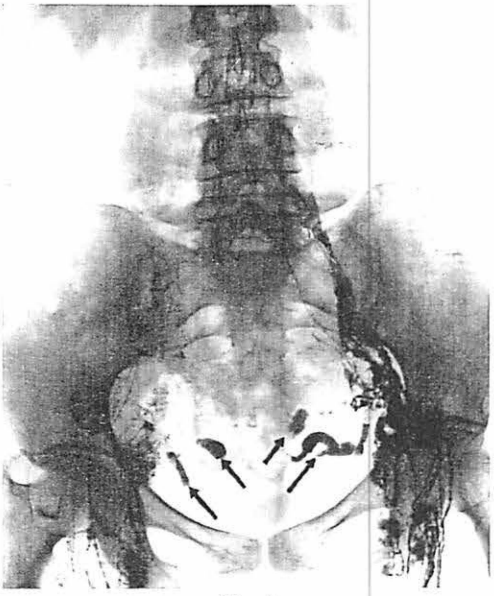

Fig. 3

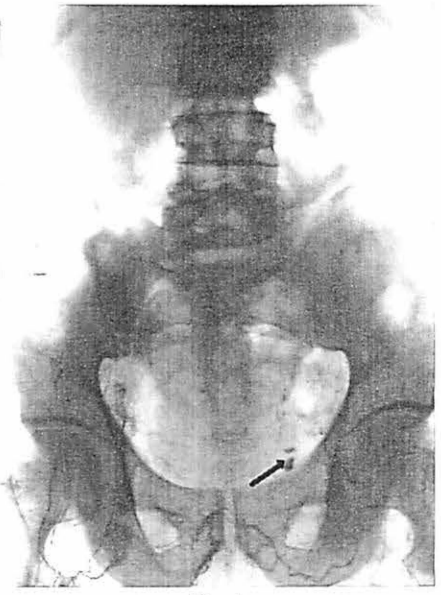

Fig. 4

Fig. 3 S. Ch. Hodgkin's disease. Stage II B prior to lymphography. Total obstruction of right lymphatic circulation, shortly (3 months) after inguinal onset of disease. Right iliac nodes almost totally replaced. No opacification of the nodes (on films taken after 24 hrs.). Numerous l.v.c. in the pelvis (arrows).

Fig. 4 D. A. Reticulum cell sarcoma. Stage II A prior to lymphography. Obstruction of left lymphatic circulation. No opacification of left iliac nodes. L.v.c. proximal to the adenopathy (arrows).

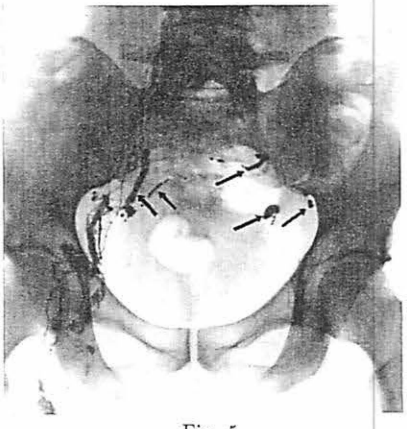

Fig. 5

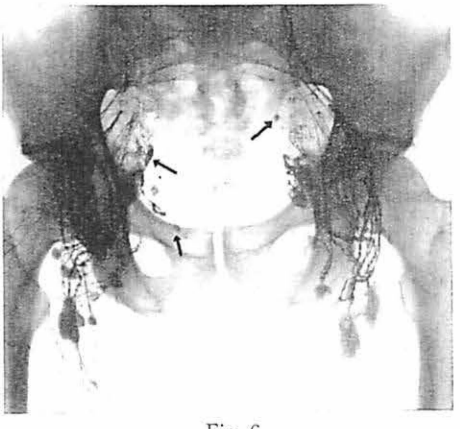

Fig. 6

Fig. 5 S. M. Reticulum cell sarcoma. Stage II B prior to lymphography; stage III after lymphography. Bilateral obstruction of lymphatic circulation. Left iliac nodes replaced. Numerous l.v.c. (arrows).

Fig. 6 N. I. Hodgkin's disease. Stage II B. Lymphography was performed after high dose irradiation of iliac nodes. L.v.c. on both sides of the pelvis (arrows).

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inguinal onset, l.v.c. are usually present: among our cases 4 of the 8 patients with l.v.c. had inguinal onset (table 2). These observations seem even more significant if the primary localisation of the disease is considered. Table 3 shows the presence of l.v.c. in 3/4 of the cases with inguinal onset.

Table 3 Relationship between the frequence of l.v.c. and the primary localization of Hodgkin's disease in the 63 cases investigated.

Primary localization	Nr. of cases	Frequence of l.v.c. (cases)
Cervical	28	0
Supraclavicular	13	2
Axillary	6	0
Mediastinal	7	1
Inguinal	4	3
Other localizations	5	0
Total	63	6

Taking into consideration the scarcity of this kind of onset – particularly in Hodgkin's disease – as well as its severe prognosis, the relationship inguinal localisation – presence of l.v.c. – poor prognosis cannot, in our opinion, be overlooked. The survival time of these patients – after lymphographic detection of l.v.c. – was very short, with rare exceptions most of the patients dying after 6 to 12 months whatever their stage was prior to lymphography. Comparing the time of survival in patients with Hodgkin's disease, we observed that patients without l.v.c. belonging to the same clinical stage as patients with l.v.c. lived much longer (table 4).

Table 4 Number and percentage of survivals over 12 months, an arbitrary period after lymphography. Comparative study on 63 patients with Hodgkin's disease at different stages, with and without l.v.c.

Stages	Survival over 12 months	
	With l.v.c.	Without l.v.c.
I.	0	2/2 – 100%
II.	2/4 – 50%	23/26 – 88%
III.	0/3 – 0%	21/28 – 75%
IV.	0/1 – 0%	3/7 – 43%

The survival time varies generally, as it is well known, according to the stage of disease and to the mode of therapy used. We have observed that patients with a dense lymphatic network capable of effective collateral flow in cases of deficiency of the main channels are more likely to have a longer survival time than those with a less dense network. When there is a progressive increase of intralymphatic pressure even the collaterals become inadequate and the l.v.c. begin to function with all the consequences they imply.

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Two cases out of 8 with l.v.c. may serve as examples. The first patient was a 51 year old male with Hodgkin's disease. Onset with right inguinal adenopathy in 1957. Admitted to a country hospital after 6 months with bilateral inguinal and iliac adenopathy without systemic symptoms. The patient was clinically classified in stage II A. Roentgentherapy was used (200 r/field). A local recurrence after 3 years was identically treated. Since 1962 he has shown polyadenopathy and associated radio- and chemotherapy was started. The disease continued to progress slowly with transient remission. The patient was admitted to our Institute in 1967 in clinical stage IV.

Lymphography was carried out in February 1967. Radiographs showed failure of node opacification, severe disturbances of lymphatic flow with numerous lymphatic collaterals and left paralumbar l.v.c. (fig. 2a and 2b); renal and vertebral bone lesions could also bee seen.

Comment: Dense lymphatic network with multiple collateral pathways. Long evolution of the disease until appearence of l.v.c. Exitus soon after detection of l.v.c.

The 67 year old female had Hodgkin's disease confirmed by biopsy. Onset in May 1967 with right inguinal adenopathy. Three months later, right iliac adenopathy. Clinical stage II B. Gynecologic examination showed uterine fibroma.

Lymphography revealed no opacification of right iliac nodes, total blockage of the lymphatic flow, no collateral lymph vessels, pelvic l.v.c. (fig. 3). Radiotherapy (3000 r/to right iliac and inguinal nodes) with associated chemotherapy gave no result. The patient died 8 months after onset of disease and 6 months after detection of l.v.c. Besides node lesions necropsy revealed kidney, spleen and liver involvement.

Comment: Rapid evolution of disease in a patient without collateral lymph pathways caused by early opening of l.v.c. Uterine fibroma and chronic adnexites in the past history may have obliterated some lymph channels. Fig. 5 shows similar case.

Radiotherapy may favour opening of l.v.c. only if administered on deep pelvi-abdominal nodes. In only one case of our 8 cases l.v.c. have occured in the pelvis after high-dose radiotherapy (fig. 6).

No major pulmonary accident has been registered – though a total quantity of 16–20 ml U.L. has been injected in all these patients. Except a single case with temperature higher than 38 °C which lasted for 48 hrs U.L. has been very well tolerated, the frequency of pulmonary embolies being no higher in patients with l.v.c. than in the others. We have excluded from our study the patients with pulmonary lesions or respiratory deficiencies.

Discussion

The l.v.c. are relatively easy to see radiologically even without cinefluorography – but their presence in malignant hemolymphopathies has not been so far sufficiently emphasized. – Some authors (2, 3, 4, 14, 15) have pointed out the accidents that the penetration of oily material into the blood might cause assuming that pulmonary embolism with clinical symptoms often occur in patients with l.v.c. This is the reason why those authors recommend cessation of contrast medium injection as soon as l.v.c. are detected. In our experience such accidents may be avoided if injection is carried out at a slow rate and does not exceed the amount of 10 ml of contrast medium for each foot.

Our most significant observation is the relation of open l.v.c. to the subsequent evolution of the disease. The fact that almost all patients have survived less than a year after lymphographic detection of l.v.c. suggests that, in certain cases of Hodgkin's disease or reticulum cell sarcomas the same process as in other node metastases may

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occur, i.e. the spread of tumor cells into the venous system owing to an early blockage of the marginal sinuses by tumor or by fibrous tissue. It seems that in malignant lymphomas this mode of spread occurs more frequently in the ilio-lumbar areas particularly when the starting point is in the inguinal nodes. In this case the rapid involvement of these areas may be due to the fact that the spread of tumor cells follows the normal route of lymph flow.

The opening of l.v.c. appears to be a consequence of increased intralymphatic pressure. *Threefoot* (14) mentions as factors favouring the l.v.c. opening the renal, hepatic and cardiac diseases as well as pleural effusions and ascites. In our opinion the renal lesions and all the other organ involvements that are sometimes observed in malignant lymphomas are partly due to spread through l.v.c. Pleural effusion and ascites have not been observed among our cases. The large number of l.v.c. detected at autopsy (51,5%) might eventually be explained by a change of dynamic conditions of lymph flow.

We should also like to point out the observation that the danger of dissemination occurs much earlier in patients with inadequate lymph flow. The absence of collateral lymphatic channels may be due either to congenital hypoplasia or to some inflammatory processes. *Malek* et al. (7) have shown experimentally that atrophy of lymphatic capillaries may follow injection of bacteria. This possibility of atrophy or fibrosis exists particularly in cases of inguinal adenopathy where infections are very common.

Whatever the explanation, the presence of l.v.c. seems to have a poor prognosis which is particularly marked in patients in whom no collaterals could be visualized. As it is well known especially in Hodgkin's disease progression is predominantly achieved by contiguous involvement of the lymphoid structures. But when the lymphatics are damaged and when even the collaterals can no longer cope with the increasing pressure, the l.v.c. begin to function and the tumor cells spread through the venous system.

These hypotheses may be questionned on several grounds. There is a general consensus of opinion that lymphography cannot detect l.v.c. until they are large enough to be radiographically visualized, therefore the failure to demonstrate them does not exclude their presence. The same can also be said in the interpretation of the radiographic picture of lymph nodes. A negative lymphadenogram does not allow us to assume that there are no microscopic lesions. But this limitation of x-ray visibility cannot detract from the value of a method which is the only one today, able to detect deep lymphatic vessels and lymph nodes in man.

However, if lymphography cannot demonstrate all l.v.c. in patients with visceral lesions nor detect the moment of their appearence we found that cases with evidence of l.v.c. had a poor prognosis. We therefore consider that patients with malignant lymphomas who besides subdiaphragmatic adenopathies also have l.v.c. belong to the stage IV of disease even if visceral lesions have not yet been detected.

Summary

Lymphatico venous communications (l.v.c.) were sought by lymphography in 122 patients with lymphomas. They were found in 6 of 63 cases of Hodgkin's disease and 2 of 12 cases of reticulum cell sarcoma. Survival was poor in patients with demonstrable l.v.c. compared to patients not

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exhibiting l.v.c. but otherwise with the same stage of the disease. It is proposed that l.v.c. favor rapid hematogenous spread of malignant cells and that patients with l.v.c. on lymphography should be classified as stage IV.

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Lymphostatic Ophthalmopathy*

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Lymphostatic encephalopathy has been described in certain patients and investigated in animal models. Among the many changes observed clinically and experimentally the alterations of the optic nerve and the papilla have not been adequately studied.

Material and Methods

In experiments performed with *Csanda* and *Zoltán* a cervical lymphatic blockade has been produced in 12 dogs.

One week after ligation of cervical lymph pathways the animals were sacrificed either by an overdose of hexobarbital or by means of decapitation. The skull was opened, the brain removed and the orbitae dissected; both eyes with the optic nerves were fixed in histological fixatives. Also the intracanalicular part of the optic nerve was used for histological studies; for this purpose, the optic nerve was transsected

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