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STAGING LAPAROTOMY FOR HODGKIN'S DISEASE

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Abstract. Splenectomy was performed in patients with Hodgkin's disease in a prospective study at the University Hospital of Umeå 1973–1978. Fifty-nine subjects were included and the laparotomy was made as a part of the pre-treatment investigation. The result of the surgical exploration was compared to other investigations, e.g., lymphangiography or cavography. The operation morbidity was 5% (3/59). The clinical stage was changed in 15/58 (26%). Fourteen upstaged and one downstaged. The macroscopical evaluation was poorly correlated to the histological involvement. It is concluded that if the staging procedure is performed by specialized surgeons the morbidity is low. No adverse effects have yet been observed after splenectomy. The staging laparotomy and splenectomy is considered superior to nonsurgical staging procedures from both treatment and cost benefit point of view.

Since 1969 when Glatstein and coworkers introduced laparotomy and splenectomy as a staging procedure in Hodgkin's disease this method has been accepted as a standard procedure in the evaluation of these patients. However, this operation has continuously been under debate (for review see Amiel & Droz, 1978; Brogadir et al., 1978; Editorial, the Lancet, 1978). The morbidity has been reported to be high and a few cases of fatal sepsis have been described (Nixon & Aisenberg, 1972; Høst et al., 1973; Chilcote et al., 1976). The overall mortality has been reported to be about 0.7% and the short term morbidity about 12% (Young et al., 1977). However, in pediatric cases the morbidity seems to be even higher. Accordingly staging laparotomy has been re-assessed in children (Aisenberg, 1978) and in adults (Bonadonna et al., 1977). Laparoscopy in combination with truecut needle biopsies have been suggested as a safer staging procedure (Bonadonna et al., 1977) and partial splenectomy has recently been suggested (Boles et al., 1978). However, none of these methods can confidently exclude occult splenic involvement (Dearth et al., 1978). Despite controversity in opinion most workers regard the surgical staging performed in specialized units as a simple and accurate investigation (Carbone et al., 1971; Dorfmann, 1971; Aisenberg & Qazi, 1974; Cannon & Nelsen, 1976; Poulsen et al., 1977). In order to assess the reliability and possible benefit of staging laparotomy compared to non-surgical staging procedures, our experiences will be presented.

MATERIAL AND METHODS

Patient selection

In a prospective study cases with untreated Hodgkin's disease diagnosed at the University Hospital of Umeå 1973–1978 were included. All patients with preoperative stage I and II (Ann Arbour classification) were included unless serious contraindications existed. Patients with stage III were included only when no severe symptoms were noted. According to Table I 3 patients with stage IV were operated on because of some doubts regarding the classification (suspect pulmonary X-ray findings or skin lesions). Thus the material consists of 59 patients, 33 males and 26 females with a mean age of 40, range 14–63 years. All patients were clinically examined with a complete work-up, including case-history, physical examination, complete blood count, liver function tests, chest X-ray, lymphangiogram, liver- and spleen scan, bone scan, needle bone marrow biopsy and in 20 cases i.v. cavography. In 58 patients the histological diagnosis was assessed by a lymph node biopsy and in one patient the preoperative diagnosis was based upon case history and a positive lymphography.

Histological classification

Sections of the original diagnostic specimen, stained with hematoxylin-eosin, were reviewed and classified according to Lukes et al. (1966). The biopsies were reviewed independently by two of the authors. When differences of opinion occurred, the sections were re-examined until a definite diagnosis was agreed upon.

Table I. *Histologic type of Hodgkin's disease versus preoperative stage*

	I	II	III	IV	A	B
Lymphocyte predominance	7	6	9	0	17	5
Lymphocyte depletion	1	1	2	0	3	1
Mixed cellularity	10	5	3	1	13	6
Nodular sclerosis	2	6	3	2	12	1
A-type	16	17	10	2		
B-type	4	1	7	1		
Total	20	18	17	3		

Lymphography

Bipedal lymphography was attempted in all cases. Lipoidol ultrafluid® 0.1 ml/kg b.wt. was injected in cannulated lymph vessels on the dorsum of the foot. In order to have a continuous flow of contrast medium an automatic injector was used with a medium injection speed of 10 ml/h injecting a maximum of 8 ml on each side. Films were taken during and after the injection of contrast medium, the same day and the day after injection. The criteria for a pathological lymphangiogram were those of Takashi & Abrams (1967) namely:

1. The foaminess of nodes was graded I–IV. Lymphonodes were regarded as pathologic when the foaminess was greater than I.
2. Filling defects; more than ⅓ of the node.
3. Para-aortic nodes; more than 2.6 cm in size.
4. Anterior spine to node distance; more than 3 cm.
5. Lateral spine to node distance; more than 2 cm.

Cavography

This examination was performed in 20 patients by injection of a total amount of 50 ml Urografin® 75% by catheters inserted into the iliac veins by Seldinger-technique. The catheters were attached by a Y-connector to an automatic injector and the contrast medium was injected within 1.8 sec.

Surgical procedure

The staging operation was performed by a standardized technique. A left upper paramedium incision was performed. The retroperitoneal space was opened and the iliac, para-aortic and para-caval lymph nodes were explored. Representative biopsies were taken and the biopsy sites were marked with clips. The next step was to explore the mesenteric and hepatoduodenal lymph nodes. Thereafter the gastrocolic ligament was opened and the lymph nodes at the upper abdominal aorta and the coeliac-axis were examined. The splenic artery was centrally ligated and splenectomy was performed including the hilar lymph nodes. The splenic pedicle was also marked with clips. The spleen was immediately cut in slices and fixed in 10% formaldehyde. A wedge biopsy was taken from the left liver lobe. In 6 cases additional fine needle biopsies were taken from both liver lobes. The staging operation was performed with atraumatic technique and no prophylactic antibiotics were used. All postoperative complications were recorded.

RESULTS

Histology

21/59 patients had lymphocyte predominance (LP) and 13/59 nodular sclerosis (NS), 21/59 mixed cellularity (MC) and 4/59 lymphocyte depletion (LD) (Table I). There was no change in histological type in any of the reviewed 58 patients, when the preoperative lymph node biopsy was compared with the histologically positive staging specimens. Twenty-three patients (39%) had splenic involvement (Table II). The liver was involved in 5/59 (9%) and positive lymph nodes were found in 25/59 (42%). All patients with liver Hodgkin also had splenic and lymph node involvement.

Lymphography (Table III) and cavography

In 2/59 patients the examination was completely unsuccessful and in 5 other patients the contrast injections could only be performed on one side. Thus bipedal lymphography was performed in 52 patients (88%). In 16 cases the lymph nodes were regarded as pathological but histologically confirmed only in 10 cases. Moreover, 5 cases showed suspect radiological changes confirmed in 4 of these patients. Thus 7 false positive findings out of 21 (33%) were recorded. In 31 cases the examination was negative although 6 histologically positive retroperitoneal lymph nodes were found. Thus 19%

Table II. *Splenic involvement versus histological type of Hodgkin's disease*

Lymphocyte predominance	8/21
Nodal sclerosis	6/13
Mixed cellularity	8/21
Lymphocyte depletion	1/4
Total	23/59

Table III. *Lymphangiography correlated to the histology of retroperitoneal lymph nodes*

Only bipedal successful examinations, $n=52$

Lymphangiography	Nodes involved	Nodes not involved
Normal (31)	6 (19.4%)	25
Suspect (5)	4 } 14	1 } 7 (33.3%)
Pathological (16)	10 }	6 }
Total	20	32

Table IV. *Hodgkin's disease, clinical stage before and after staging laparotomy*

Stage	Before laparotomy	After laparotomy
I+II	38	28
III	17	23
IV	3	8
Not staged	1	

false negative lymphangiograms were recorded. To sum up 75% of the successful bipedal lymphographies were proven to be correct.

Two out of 20 cavographies were correctly recorded as positive.

Surgical staging

The operation morbidity was 3/59 (5%) represented by intra-abdominal postoperative hemorrhage requiring reoperation (1), subdiaphragmatic abscess (1) and leftsided pleuritis (1). No mortality occurred.

The clinical stage pre- and postoperatively is shown in Table IV. Before laparotomy 38/58 (65%) of the patients were classified as stage I or II. This was reduced to 28/58 (48%) postoperatively. Twenty out of 58 (34%) patients were classified as stage III or IV preoperatively and 31/58 (53%) after laparotomy. One patient without preoperative biopsy was postoperatively staged as IIB. When individual cases were analysed 9/58 were upstaged from I+II to III, and another 2 to stage IV. Moreover, 3 out of 58 patients were upstaged from stage III to IV (Table V). Thus a total of 14/58 (24%) were upstaged. One of the patients were downstaged from stage III to II. Unless major changes were found the macroscopical evaluation was poorly correlated to the histological involvement (Table VI).

The mean treatment time at the surgical ward was 7 days (range 2–29 days). However, the total mean pre-treatment time including the surgical staging was 33 days (range 25–130).

DISCUSSION

Staging laparotomy for Hodgkin's disease has been criticized for various reasons. Disadvantage such as high postoperative morbidity has been pointed out (Bonadonna et al., 1977; Brogadir et al., 1978; Young et al., 1977). The short-term morbidity varies according to these authors from about 12 to 37%. However, most of these complications are minor, e.g. pleuritis, atelectasis, bronchopneumonia or wound infections. More serious complications such as intraperitoneal bleeding or subphrenic abscesses requiring re-operation have been reported. The mortality is less than 1%. In our material the total postoperative complications amounted to 5% which is in accordance with other Scandinavian reports (Høst et al., 1973; Poulsen et al., 1977). Even though one of our patients had to be reoperated the mean hospitalization period at the surgical ward was only 7 days or about 20% of the mean pretreatment hospitalization time.

At the staging operation the surgeon recorded whether lymph nodes, spleen or liver were engaged by Hodgkin's disease by a thorough examination including the observation of the cut surface of biopsy samples. The staging operation was of special value with regard to intra-abdominal lymph nodes not visualized by lymphography. Only major changes, however, could be distinguished macroscopically and even so a poor correlation was found

Table V. *Cause of postoperative change in stage*

Preop. stage	Postop. stage	No.	Comments
I+II	III	9	Lymph node pos. (3) Spleen pos. (1) Lymph node and spleen pos. (5)
	IV	2	Lymph node, spleen and liver pos.
III	IV	3	Liver pos.
	II	1	Lymph node neg.
Not staged	II	1	Spleen pos.
Total		16/59 (27%)	

Table VI. *Accuracy of macroscopical staging*

	Liver		Spleen		Lymph nodes	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Macroscopically	44	10	30	24	34	19
Histologically	3	1	5	16	8	14

to the histological findings. Thus obviously, a reliable diagnosis of lymph node involvement is virtually impossible without systematic multiple biopsies. The same observation was also done in many cases of suspected splenic or liver involvement.

In agreement with other authors we found that ⅓ of the patients had splenic involvement histologically. Although the spleen was regarded macroscopically normal, microscopical foci of Hodgkin's disease were found in about 20% (cf. Dearth et al., 1978). Therefore we regard laparoscopy with random truecut biopsies, suggested by Bonadonna et al. (1977), as inferior to staging laparotomy to exclude occult disease. Furthermore, by the former method severe intra-abdominal hemorrhage occurred in about 3% (Bonadonna et al., 1977). In conclusion, we regard staging laparotomy with splenectomy as a safer and more reliable diagnostic procedure when performed by specialized surgeons.

The opinions of the diagnostic accuracy of lymphography as a staging procedure varies between different centers. In our hands 75% of the successful bipedal examinations were histologically proven to be correct. Cotman et al. (1977) claim an 85% overall accuracy in Hodgkin's disease. However, in about 20% of their cases the lymphography was falsely positive or negative. This is in accordance with the findings reported by Glatstein et al., 1969, (18%) and by our group in the present study (25%). Thus a correct staging of retroperitoneal lymph nodes cannot be performed with lymphography in one out of four to five patients. Furthermore, occult intra-abdominal lymph node involvement cannot be diagnosed. Complications have been reported to occur following lymphography, e.g. pulmonary bleeding (Margling & Castellino, 1979). Furthermore there is always a risk of oil embolism and pneumonitis. Studies after lymphography have accordingly shown a transient impairment of the pulmonary function although the patients did not show any respiratory symptoms (Hultén et al., 1966). This observation, however, may explain some cases of pneumonia occurring after staging operations in patients previously examined with lymphography.

In our center we have adopted a highly selected treatment based on the extension of the disease (radiotherapy with mantle, mantle-Y, total nodal irradiation, chemotherapy or combination therapy—especially in bulky disease). For this reason we consider staging laparotomy with splenectomy, being the most accurate method to diagnose occult subdiaphragmatic disease, as necessary to determine the definite treatment policy.

It is satisfactory to point out the very low morbidity and the lack of postoperative mortality in the present study. Furthermore, we have not observed any adverse effects after splenectomy compared to what is seen in non-splenectomized patients. However, a possible long-term difference with regard to infections and survival in splenectomized patients receiving intensive chemotherapy and/or irradiation cannot be excluded. This possibility has to be further studied in major prospective randomized studies.

In conclusion we find the diagnostic reliability of staging laparotomy and splenectomy superior to non-surgical staging procedures from treatment as well as cost benefit point of view.

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Short Communications

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Acute Leukaemia after Prolonged Chlorambucil Treatment for Non-Malignant Disease: Report of a New Case and Literature Survey

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Key Words. Chlorambucil · Acute leukaemia · Immunosuppressive agents

Abstract. A case of acute myeloblastic leukaemia is reported in a patient treated with chlorambucil during 72 months for multiple sclerosis. In a review of the medical literature, 43 additional reports of acute leukaemia after chlorambucil therapy for non-malignant diseases were found. Most cases are of a non-lymphoid type and preceded by various blood and bone marrow abnormalities. The prognosis is poor with a short survival. The risk of developing acute leukaemia after long-term immunosuppressive treatment with chlorambucil is emphasized.

Chlorambucil, an alkylating agent with immunosuppressive properties, has been used for the treatment of a wide spectrum of non-malignant conditions. Its leukaemogenic action on such patients has been recently emphasized [4]. We report a new case of acute myeloid leukaemia in a patient treated with chlorambucil for multiple sclerosis.

Case Report

A 20-year-old woman was just evaluated in 1960 for a recent history of diplopia and rapid loss of vision in the right eye. The diagnosis of multiple sclerosis was in little doubt and a treatment was started with synthetic corticotrophin given intrathecally and intravenously. In December 1969 the patient developed a rapidly progressive weakness of the right leg and she was placed on chlorambucil, 6 mg daily. Frequent haematologic controls failed to reveal cytopenia but chlorambucil was discontinued in 1976. The cumulative dose was about 10 g during an overall period of 72 months.

From 1976 to 1978, the patient frequently experienced episodes of fatigue, fever and urinary infection. In October 1978, a macrocytic anaemia occurred with thrombocytopenia. Leukopenia with granulocytopenia occurred in November 1978.

The patient was referred to us, in January 1979, because of pancytopenia (Hb = 9.9 g/dl, WBC = 3.3×10^9/l, platelets = 50×10^9/l). Physical examination showed skin pallor without jaundice. There was no enlargement of the spleen, liver or lymph nodes. The bone marrow sternal aspirate displayed normal cellularity, megaloblastoid changes of the erythroid series and abnormal myeloid maturation with increased percentage of myeloblasts (18%). Auer rods were not present. The reaction for myeloperoxidases was positive. The reaction for non-specific esterases was positive,

unaffected by exposure to sodium fluoride. No ringed sideroblast was seen with the Perls staining. Bone marrow culture in agar, using the technique of *Pike and Robinson*, showed a normal pattern of growth. Bone marrow cells karyotype was not performed. The patient was discharged without any treatment.

A low percentage of myeloblasts on blood counts appeared in February 1979. The bone marrow myeloblasts count rose to 45% in March 1979. The diagnosis of acute myeloid leukaemia was established, M_1 type according to the FAB group classification [1]. Intensive chemotherapy was started with vincristine, cytosine arabinoside and daunorubicin. This treatment resulted in severe marrow aplasia leading to a rapid fatal outcome.

Discussion

Chlorambucil has been widely used for immunosuppression in various autoimmune or inflammatory diseases. We were able to collect, mainly from the references indexed in the *Index Medicus* of the National Library of Medicine, 43 additional cases of acute leukaemia occurring after prolonged chlorambucil treatment for non-neoplastic diseases [2–14]. Among the 44 patients there were 10 males, 33 females and 1 patient for whom sex was not specified. The underlying diseases included rheumatoid arthritis (18 cases), glomerulonephritis and nephrotic syndrome (8 cases), multiple sclerosis (8 cases), psoriatic arthritis (4 cases), Wegener's granulomatosis (2 cases), progressive systemic sclerosis (1 case), juvenile rheumatoid arthritis (1 case), malignant exophthalmos (1 case), Behçet's disease (1 case).

The mean duration of chemotherapy was 35 ± 22 months (42 cases available – range 3–98 months), and the mean cumulative dose of chlorambucil was 5.8 ± 3.9 g (35 cases available – range 0.3–18 g).

The mean interval from discontinuation of cytotoxic chemotherapy to leukaemia was 38 ± 28 months (39 cases available – range 1–132 months). Various blood abnormalities were commonly encountered during this preleukaemic phase, including pancytopenia, neutropenia, macrocytic anaemia, thrombocytopenia, monocytosis or mild myeloid leukaemoid reaction. Most of the 12 patients for whom bone marrow pictures were available exhibit increased cellularity with marked dysmyelopoiesis: cytologic abnormalities involved the three lines, but erythroblastic changes were most striking. The cytological type of leukaemia is known in 43 cases. Most of these were of the myeloid types (37 cases). Response to antileukaemic therapy was poor. The mean duration of survival from onset of leukaemia was 2 months (24 cases available – range 0–8 months).

Finally, regarding its leukaemogenic action, the prolonged use of chlorambucil for non-neoplastic diseases should be discouraged, certainly restricted to severe, life-threatening forms.

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