Lymphology 22 (1989) 100-102

HISTOLOGIC CHANGES IN DOG LYMPH NODES AFTER ENDOLYMPHATIC APPLICATION OF BLEOMYCIN OIL SUSPENSION

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ABSTRACT

Bleomycin oil suspension (Oil-Bleo) was injected endolymphatically in a dog experiment. The drug remained in lymph nodes over many weeks in detectable concentrations. The histologic changes in these lymph nodes were examined and compared with 3 controls (aqueous Bleomycin, Lipiodol, and no treatment). Granulomatous reaction, microabscesses, and small necrotic foci were observed. After a month, fibrosis was detectable in all lymph nodes. The damage to microscopic lymph node structures after Oil-Bleo was moderate. These findings suggest that Oil-Bleo may be useful in local treatment of lymph node metastases.

In a previous report (1), the potential usefulness of cytostatics deposited in dog lymph nodes was explored. After endolymphatic application of Oil-Bleo (Bleomycin oil suspension, research sample supplied by the Nippon Kayaku Co., Tokyo), the Bleomycin concentration in serum, urine, lymph, and lymph nodes was examined. It was found that Bleomycin remained in lymph nodes in high concentrations over a long period of time and that the macroscopic structure of these nodes was preserved. The histologic changes in lymph nodes after the deposition of Bleomycin suspension are now reported.

MATERIALS AND METHODS

For the main experiment, 7 young related bastard dogs with a weight of 13±1.5kg were used. Each dog received an endolymphatic application of 4ml Oil-Bleo (60ml Bleomycin). The injection site was a lymphatic vessel between the dorsal side of the foot and the shank. The infusion time was one hour.

One main and 3 control groups were examined (*Table 1*). The lymph nodes were excised at intervals of up to 28 days after injection. One-half of each lymph node was fixed for histological examination and the other half was homogenized to determine the Bleomycin concentration. Sixty-three lymph nodes, including those of the controls, were examined histologically.

RESULTS

Lymph node enlargement after treatment correlated with Oil-Bleomycin concentrations in the nodes. Lymph nodes with a high Bleomycin content were up to two times heavier than the corresponding untreated control nodes. The treated nodes showed no macroscopic signs of toxic or mechanical damage.

The microscopic findings in Bleomycin-treated lymph nodes are best understood when compared with lymph nodes

Table 1
Lymph Nodes Examined: Experimental Groups

Group	Injection With	Removal Time (Days After Injection)	Number of Lymph Nodes Examined
1.1		1	5
1.2	Oil	7	12
1.3	Bleo	14	13
1.4		28	8
2	Aqueous Bleomycin	¼	4
3	Lipiodol	7	13
4	No Treatment	0	8

after normal diagnostic lymphography with Lipiodol Ultra-Fluid (iodized oil, Byk Gulden, West Germany).

The main histological alterations in those two groups are shown in *Table 2*. The nodes were removed on the 7th day after injection. The most important finding was that the Bleomycin group had 3 times more necrotic foci; the effect of this micronecrosis is fibrosis. Both alterations can exist in neighboring areas of a lymph node. Every second node was, however, free of necrosis.

The rate of granulocytic reaction with microabscesses was similar in both groups. An extensive tissue compression with oil droplets was seen in each lymph node.

All the alterations reported above were reversible, although fibrosis persisted. This fibrosis was slight and did not lead to the obliteration of lymph nodes. The oil droplets, which dominated the histological picture after injection, were reduced in amount and size after 4 weeks *(Fig. 1)*.

Table 2
Lymph Node Comparison in Therapeutic and Diagnostic Lymphography

	Oil-Bleo	Lipiodol
Days after Injection	7	7
Number of Lymph Nodes Examined	12	13
Histologic Alterations		
Micro-abscess	3/12 (25%)	4/13 (31%)
Necrotic Foci	6/12 (50%)	2/13 (15%)
Fibrosis	9/12 (75%)	1/13 (8%)

COMMENT

Bleomycin oil suspension remains in lymph nodes in the form of oil droplets for many weeks in high concentrations. The toxicity for lymph node tissue is higher than after pure Lipiodol (2-4) but still remains moderate. Macroscopically, only lymph node enlargement is evident. The histological alterations are reversible. The only long-term expected effect is slight fibrosis. On the other hand, mild fibrosis is also common in untreated lymph nodes and thus to a certain extent represents a normal physiological response of these particular lymph nodes.

These findings indicate that Oil-Bleo may be useful as a cytostatic agent in local treatment of lymph node metastases.

ACKNOWLEDGEMENT

Supported by Deutsche Stiftung für Krebsforschung, Bonn, West Germany.

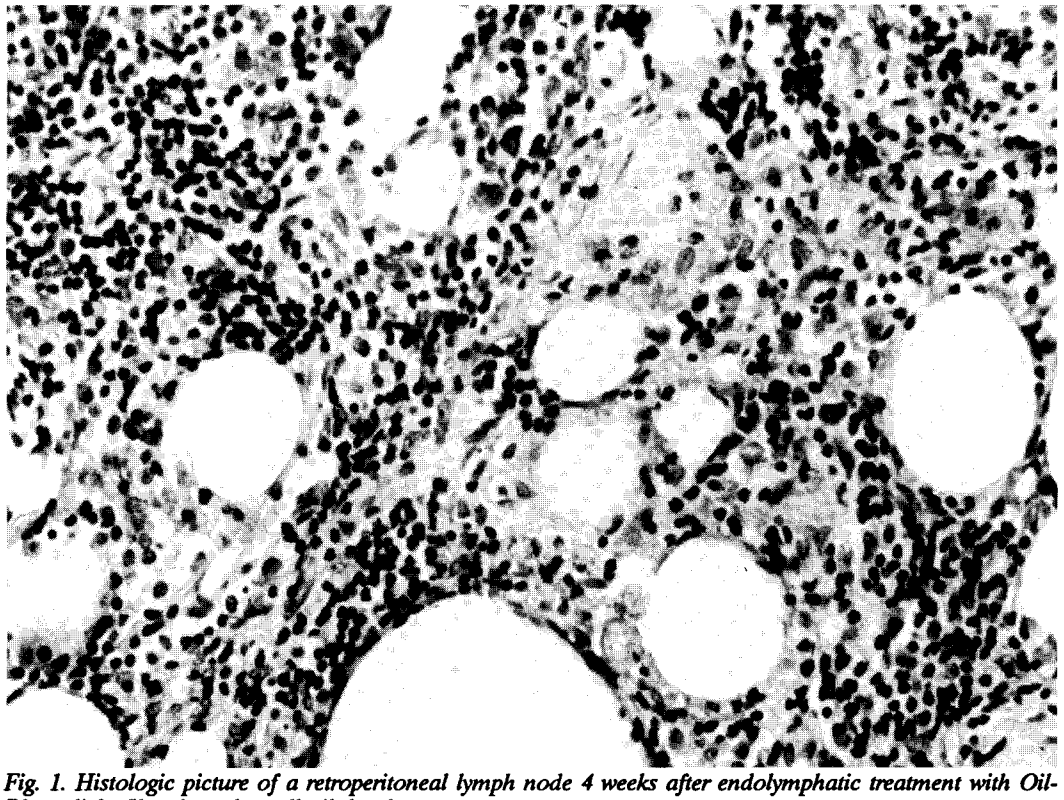

Fig. 1. Histologic picture of a retroperitoneal lymph node 4 weeks after endolymphatic treatment with Oil-Bleo: slight fibrosis and small oil droplets.

REFERENCES

1. Hirnle, P: Endolymphatic application of Bleomycin oil suspension in dog model. Lymphology 18 (1985), 56.
2. Gregl, A, J Kienle, J Stelzner, et al: Morphologische veränderungen in den lymphknoten nach lipiodollymphographie. Fortschr. Röntgenstr. 110 (1969), 297.
3. Lüning, M, M Wiljasalo, H Weissleder (Eds.): *Lymphographie Beimalignen Tumoren.* Thieme, Leipzig (1976)
4. Ravel, R: Histopathology of lymph nodes after lymphangiography. Am. J. Clin. Path. 46 (1966), 335.

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