

DIAGNOSTIC SIGNIFICANCE OF MAST CELLS IN ABNORMAL UTERINE BLEEDING

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Abnormal uterine bleeding is one of the frequent gynaecological disorders. Proper treatment of the condition requires determination of the exact aetiological basis of the lesion, and, for want of this, normal organs are too often sacrificed by surgery or rendered functionless by X-ray exposure.

Rumbolz and Greene (1957) examined human endometrium for the presence of mast cells and reported an increase in the number of these cells throughout the secretory phase of the menstrual cycle and also in pregnancy and certain bleeding stages associated with a secretory endometrium. They believe that the mast cells in the endometrium could serve as a source of locally available heparin which mixes with menstrual blood and produces free bleeding. This observation offered a rationale for anti-heparin drugs such as toluidine blue and protamine sulphate in treating certain cases of menorrhagia. The object of the present study is to

assess the role of mast cells in abnormal uterine bleeding.

Material and Methods

The curettage or hysterectomy specimens were obtained from 125 patients admitted to Rajindra Hospital, Patiala and the attached Lady Dufferin Hospital. Most of the cases included complained of dysfunctional uterine bleeding, sterility or miscarriage.

The endometrium after fixation in 10% formal-saline was processed for paraffin sections which were stained with toluidine blue by the modified method of Holmgren (1938). The technique adopted differed from the original in that 0.5% aqueous solution of toluidine blue instead of 1% was employed and the sections were mounted in water instead of canada balsam. With this modification, the mast cells were made more prominent and could be readily counted. In addition, the sections were also stained with haematoxylin and eosin for determining the histopathological condition.

An exact count of the number of the mast cells in a section of the endometrium is practically impossible. It has, therefore, been necessary to ap-

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proximate the number of cells, grading them from 0 to 3+ according to the number seen per high power field. Five or more scattered fields were examined in each slide and an average worked out. One to three mast cells per high-power field were graded as one plus (1+), four to six cells as two plus (2+), and seven or more cells as three plus (3+).

Results

Table I gives the details of the histological observations made on endometrial tissue from 125 cases.

Of the 19 cases clinically considered as normal, 9 showed secretory endometrium. In 10 the endometrium was in proliferative phase. Of the 29 cases giving a history of an increase in the amount or duration of menstrual flow, 9 had a secretory endometrium and 20 had proliferative type. Of the 64 cases with the complaint of irregular menstrual flow, 19 had proliferating endometrium, 22 showed a proliferative phase with tendency to dilatation of glands and 17 had cystoglandular hyperplasia of the endometrium. Only 6 had a secretory phase. Of the 3 cases with clinical diagnosis of uterine polyps, two had leiomyomatous polyps while one had endometrial polyp. The remaining cases comprised of adenomyosis (one), adenocarcinoma of the endometrium (one), tuberculous endometritis (one), hydatidiform mole (two), and pregnancy (five); the tissues in the pregnant cases were obtained at the time of evacuation of the uterus following spontaneous abortion.

The clinically normal group of cases with secretory endometrium

showed 1+ mast cells in 4, 2+ cells in 2, and 3+ in 2 cases while only in one case the mast cells were absent. The normal cases with proliferative endometrium showed 1+ cells in 5, 2+ in 1 case and none in the remaining 4.

All the 29 patients with diagnosis of menorrhagia showed mast cells in the endometrium. Of the 9 cases of secretory phase endometrium, 5 were graded as 3+, 3 as 2+ and 1 was graded as 1+. Of the 20 cases of proliferative endometrium, 5 were graded as 3+, 12 as 2+ and only 3 showed 1+ cells.

The 64 cases of metrorrhagia showed markedly diminished number of mast cells as compared with the preceding group. Of the 6 cases of secretory endometrium, 4 were graded as 1+, 1 as 2+ and the remaining 1 as 3+. Of the 19 cases of proliferative endometrium 9 cases were graded as zero and 8 as 1+ and only 2 were considered as 2+. Of the 22 cases of proliferative endometrium with tendency to dilatation of the glands, 7 cases were graded as zero and 14 as 1+ and only 1 was considered as 2+. Of the 17 cases of cystoglandular hyperplasia, 6 were graded as zero and 11 as 1+.

In the pregnancy group, 4 of the 5 cases were graded as 2+ or 3+ and only 1 as 1+. The case of adenomyosis of the uterus was graded as 3+. In the case with endometrial adenocarcinoma, the mast cells were graded as 2+. The case of tuberculous endometritis showed no mast cells.

Of the 3 cases of polyps, 2 were graded as 2+ while the remaining as 3+. The cases of hydatidiform mole

were graded as 1+ and 2+ respectively. (1950); Sylven (1951) and Rumbolz & Greene (1957). Similarly, our in-

TABLE I
Histopathological Diagnosis and Mast Cells Correlation

Symptoms and findings	No. of cases	Absent	Mast cells		
			1+	2+	3+
Normal menstruation (19 cases)					
Secretory endometrium	9	1	4	2	2
Proliferative endometrium	10	4	5	1	—
Menorrhagia (29 cases)					
Secretory endometrium	9	—	1	3	5
Proliferative endometrium	20	—	3	12	5
Metrorrhagia (64 cases)					
Secretory endometrium	6	—	4	1	1
Proliferative endometrium	19	9	8	2	—
Proliferative phase with tendency to dilatation of glands					
Cystoglandular hyperplasia	22	7	14	1	—
.. .. .	17	6	11	—	—
Pregnancy					
.. .. .	5	—	1	2	2
Adenocarcinoma					
.. .. .	1	—	—	1	—
Adenomyosis					
.. .. .	1	—	—	—	1
Hydatidiform mole					
.. .. .	2	—	1	1	—
Tuberculous endometritis					
.. .. .	1	1	—	—	—
Polyps (3 cases)					
Leiomyomatous polyp	2	—	—	2	—
Endometrial polyp	1	—	—	—	1

1 + denotes — one to three mast cells/high power field.

2 + denotes — four to six mast cells/high power field.

3 + denotes — seven or more mast cells/high power field.

Discussion

In histologically normal endometrium from patients with physiological menstrual cycle very few mast cells were seen during the proliferative phase; they, however, increased during the secretory period. These observations conform with those of Asplund & Holmgren (1947); Wislocki & Dempsey (1948); McKay

investigations show that the concentration of the mast cells was increased in the endometrium in patients with menorrhagia as compared with the normals, during the same stage of the menstrual cycle. These findings agree with those of Rumbolz & Greene (1957).

The mast cells were markedly lowered in cases of metrorrhagia.

This observation is corroborated by the work of Rumbolz & Greene (1957). In the present investigation an increase of mast cell was noted in pregnancy and in endometrial neoplasms. Our findings in pregnancy agree with those of Asplund & Holmgren (1947) and Rumbolz & Greene (1957).

Allen and his associates (1949 a, c) treated successfully a number of patients complaining of abnormal uterine bleeding with toluidine blue and protamine sulphate. Elghammer et al (1949); Rumbolz et al (1952); Lathrop & Carlisle (1952); Chesley et al (1953); Jacobs and Lindley (1956) and Scholz (1956) have subsequently reported on the successful use of anti-heparin drugs in treating abnormal uterine bleeding. Allen et al (1949b) opined that the action was one of neutralizing an excess of circulating anticoagulant, most likely heparin, but no explanation as to the origin of this anticoagulant was offered.

Latta and Beber (1953) while investigating the histological characteristics of the human placenta by various histochemical techniques, found mast cells in the mesodermal core of the chorionic villi of all the 14 placentas examined which ranged in age from 3½ weeks to full-term. The authors postulated that the metachromatic eosinophilic granules in the mast cells represented heparin or heparinoid substances to be associated with incoagulable, free flowing blood in such locations where one might assume it would clot. It was further suggested that similar cells in the endometrium could serve as a source of locally available heparin

which mixes with menstrual blood and produces free bleeding. This possibility offered a rationale for anti-heparin drugs in treating certain cases of menorrhagic bleeding.

The presence of the mast cells in the human uterus had been described as early as 1897 by D'Erchia. Huguenin (1912); Geist (1913); Staemmler (1921); Nurnberger (1925) and Stieve (1929) described that the mast cells were very scanty in the endometrium, but more abundant in the connective tissue and in the myometrium especially in the neighbourhood of the large blood vessels. Weill (1921) reported the presence of the mast cells in the human endometrium and observed them in early pregnancy. von Numers (1942) reported a relative increase of the number of mast cells in the human endometrium during the proliferative phase. During the secretory phase no mast cells were visible in the superficial parts of the endometrium while they increased in the basal layer of the stroma.

The consensus of opinion at present is that the mast cells are the source of heparin in the endometrium, and this can explain certain cases of heavy or prolonged menstrual bleeding associated with secretory endometrium. Marked increase of this anti-coagulant in the blood can be demonstrated by an elevated protamine titration. Lesser degree of heparin excess can cause a local effect with increased bleeding and still not produce systemic manifestation. It seems that anti-heparin drugs like toluidine blue and protamine sulphate have a direct neutralising effect on increased number of heparin-

bearing granules in mast cells. Bickers & Richmond (1953) and other authors have concluded from the histologic evidence and clinical response that toluidine blue is of the greatest value in cases of menorrhagia associated with normal ovulation and normal secretory endometrium. Little or no response could be demonstrated in cases of organic diseases even though the number of mast cells appeared to be increased in certain instances. Whenever feasible, protamine titration and the study of the mast cells in the endometrium are valuable adjuncts to effective therapy. Before starting the treatment with antiheparin drugs it is essential that the cases for this therapy be selected and the presence of an unsuspected malignancy excluded.

Summary and Conclusion

1. Endometrial specimens obtained from one hundred twenty-five cases were studied for the presence of the mast cells.

2. An increase in the number of the mast cells was observed from the time of ovulation throughout the secretory phase.

3. The cases of menorrhagia showed greater number of mast cells than were observed in the normal cases at the same stage of the cycle.

4. The cases of metrorrhagia showed far fewer cells than the preceding group.

5. The cases of pregnancy and various tumours of the endometrium also showed increased number of mast cells.

6. These mast cells are considered to be the readily available source of heparin in the endometrium which

mixes with the menstrual blood and produces free bleeding.

7. The increase in the number of the mast cells in cases of menorrhagia can explain the heavy or prolonged bleeding in these cases. This offers a rationale for the antiheparin therapy in certain cases of menorrhagia.

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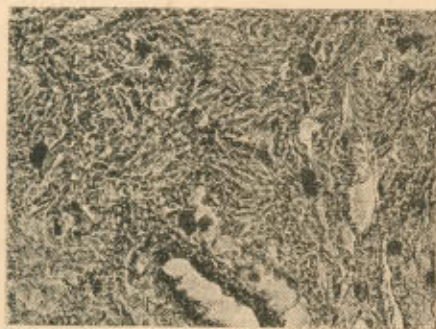


Fig. 1
Paraffin section from an endometrial polyp
showing 3+ mast cells. Toluidine blue x 400.