MAST CELLS IN ABNORMAL UTERINE BLEEDING

by

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Abnormal uterine bleeding is one of the commonest disorder in the female, which needs thorough investigation to ascertain the exact aetiological basis so that a proper treatment can be rendered to such cases.

Rumbolz and Greene (1957) studied mast cells in the endometrium in different physiological and pathological conditions and observed definite increase of mast cells in the secretory phase, decidua of pregnancy and certain cases of dysfunctional uterine bleeding associated with the secretory endometrium. Similar observations were also made by Saigal and Balasubramanyan (1963) in patients with dysfunctional uterine bleeding with secretory endometrium as well as in patients after abortion. But Mehra *et al* (1970) in their study found no definite relationship of mast cell count in the endometrium with dysfunctional uterine bleeding, except in those cases following complete or incomplete abortion.

From these observations, it was suggested that presence of metachromatic granules of the mast cells in the endometrium serve as the ready source of locally available heparin which mixes with the menstrual blood and produces free bleeding and a rationale was offered for the use of antiheparin therapy, such as toluidine blue and protamine sulphate in treating these cases.

The purpose of the present study is to assess the association of mast cells in the uterus with abnormal uterine bleeding in various obstetrical and gynaecological conditions.

Material and Methods

Endometrial currettage, biopsy and hysterectomy specimens were obtained from 270 cases admitted into the Assam Medical College Hospital, complaining of abnormal uterine bleeding, along with 100 cases representing control group with history of normal menstruation and in which no pathological lesion was detected.

The specimens were fixed in 10% buffered formol-saline and after processing, paraffin sections of 5 micron thickness were stained with 0.5% aqueous solution of toluidene blue, dried and mounted in D. P. H. In addition sections were stained with haematoxylin and eosin in order to determine any histopathological changes. After the study of general pathological changes in H. and E. preparations, mast cells were counted in sections stained with toluidine blue under the 10 X eye piece and 43 X high power objective of the light microccope. The size of the visual field was 2.17 sq. mm. The mast cells were counted

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in five representative fields in each section and average number per field were calculated.

Results

The histological groupings and the average number of mast cell distribution per high power field in 100 cases of normal controls and in 270 cases of abnormal uterine bleeding are summerised in Tables I and II, respectively. In the normal group the number of mast cells was the highest in the myometrium, in the cervix and the least in the endometrium (Table 1 and Fig. 1). They were more numerous in the deeper part of the endometrium towards the basal layer, particularly in the secretory phase, mostly in the neighbourhood of the endometrial glands and blood vessels (Fig. 3). In the stroma, mast cells were rarely found, only a few were seen surrounding the areas of haemorrhage. A few mast cells in the late secretory phase were seen in the process of degeneration with discharge of their granules into the surrounding stromal tissue.

It is evident from Table II that the average mast cell number in the endometrium was higher in the menorrhagia than in the metrorrhagia group (Fig. 2). However, taking into consideration the

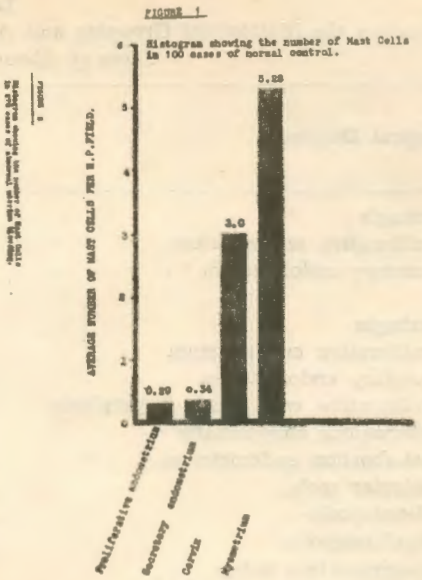

Fig. 1
Histogram showing the number of mast cells in 100 cases of normal controls.

histological findings, mast cell number was highest in endometrial polyp in metrorrhagia cases and next in decidua of pregnancy (Fig. 4) and the least in tuberculous endometritis. In the proliferative and secretory endometrium of menorrhagia and metrorrhagia cases mast cells were increased and were found deep around the glands, blood vessels, areas of haemorrhage and chronic inflammatory foci. In the endometrial tissue, those showing cystic hyperplasia and haemor-

TABLE I

Showing the Histological Groupings and Average Number of Mast Cells in 100 Cases of Normal Controls

Histological findings	Clinical history	No. of cases	Average No. of mast cells/HPF
Endometrium			
Proliferative	Sterility	50	0.29
Secretory	Sterility	30	0.34
Cervix	Cases without any history of abnormal bleeding	10	3.0
Myometrium		10	5.28

TABLE II

Showing the Histological Grouping and Average Number of Mast Cells per HPF in 270 Cases of Abnormal Uterine Bleeding

Histological Diagnosis	Total No. of cases	No. of cases	Average No. of mast cells per HPF
Menorrhagia	80		
Proliferative endometrium		50	0.76
Secretory endometrium		30	0.60
Metrorrhagia	190		
Proliferative endometrium		50	0.30
Secretory endometrium		30	0.44
Proliferative with cystic hyperplasia		10	0.50
Tuberculous endometritis		5	0.08
Post-abortion endometrium		30	1.04
Vesicular mole		10	0.18
Adenomyosis		10	2.64
Fibroleiomyoma		25	4.12
Leiomyomatous polyp		10	4.12
Endometrial polyp		10	1.24

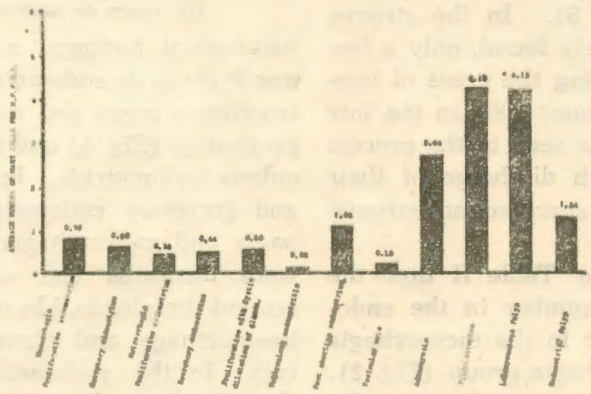

Fig. 2
Histogram showing the number of mast cells in 270 cases of abnormal uterine bleeding.

rhages contained comparatively more mast cells than in those with proliferative and secretory patterns (Fig. 5).

In the myometrium, the mast cell number was comparatively less in metrorrhagia group than that of normal cases. In the metrorrhagia group largest number of mast cells were found in fibroleiomyoma and adenomyosis (Figs. 6 and 7). In the cervix, mast cell number in leiomyomatous polyp in metrorrhagia cases was much higher in comparison to the normal cervix. The mast cells were concentrated underneath the squamous epithelium, mostly around the blood vessels and amongst the area of chronic inflammation (Figs. 8 and 9). Again without taking into consideration of histological

grouping, mast cell number was found to be high in the cervix and myometrium and low in the endometrium in the metrorrhagia group. In the myometrium mast cells were present more towards the serous surface and were comparatively more in the area of loose connective tissue than in the muscle tissue (Fig. 10) and were particularly more around the blood vessels. In fibroleiomyoma large number of mast cells were seen in the normal myometrium surrounding the growth. But, in the growth itself the number of mast cells was less. Moreover, in the growth itself fibrous tissue element contained less number of mast cells than in the muscle tissue. Mast cells were comparatively higher in the subserous and submucous types than in the interstitial type. Increased number of mast cells were found in the areas of growth associated with chronic inflammation, haemorrhage, hyaline degeneration and necrosis.

In the cases with adenomyosis, increased number of mast cells were observed in the muscle tissue than in the endometrial tissue.

In the recent years much attention has been focussed on the study of tissues in various pathological conditions. The presence of mast cells in the uterus and other pelvic organs has been noted for a long time, but the relation of these cells to uterine bleeding has been stressed only recently (Rumbolz and Greene, 1957; Saigal and Balasubrahmanyan, 1963) which may change the rationale of treatment of uterine bleeding in these cases. Mast cells are the main source of heparin and are responsible for the prevention of blood coagulation and maintenance of the blood in a fluid state in various pathological conditions (Janes and McDonald, 1948). The authors postulated that increased mast cells in the uterus lead to an increase of locally available heparin, which becomes mixed with the menstrual blood and produce free bleeding.

In histologically normal endometrium from the control cases with normal menstrual cycle, a few mast cells were observed during the proliferative phase but they were slightly increased during the secretory phase. These observations are in agreement with those of Asplund and Holmgren (1947), Wislocki and Dempsey (1948); Rumbolz and Greene (1957); Saigal and Balasubrahmanyan (1963) and Fox and Abell (1965). In some of the cases with late secretory endometrium, few mast cells were found in the process of degranulation with discharge of their granules—a finding which was also reported by Vara (1962).

The endometrium in cases with menorrhagia, the concentration of mast cells were seen to increase in both proliferative and secretory phases as compared with the normal controls during the same stage of menstrual cycle. Rumbolz and Greene (1957) and Saigal and Balasubrahmanyan (1963) also reported similar findings. Similarly, in the endometrium of patients with menorrhagia, the average mast cell count was found to be increased as compared with the normal control group. But less concentration of these cells were found in metrorrhagia than in menorrhagia. Such a finding is in contradiction to the reports of Rumbolz and Greene (1957) and Saigal and Balasubrahmanyan (1963). The increase of mast cell population in metrorrhagia cases in the present series can be due to the presence of haemorrhage and chronic inflammatory foci which were commonly associated in these conditions. The average mast cell number in cases

of endometrial tuberculosis in metrorrhagia group was found to be very low. This observation is similar to that of Saigal and Balasubrahmanyan (1963). But Janes and McDonald (1948) reported increase of mast cells in tuberculous lesions of the synovial membrane. Endometrial polyps showed increased number of mast cells when compared with that of normal endometrium. These findings are in agreement with those of Staemmler (1921) and Saigal and Balasubrahmanyan (1963). Many workers, like Harris (1900), Staemmler (1921), Tinel and Vimeux (1952), Latta and Beber (1953) and Beber *et al* (1960) reported scanty mast cells in human placenta and practically absence of any mast cells in the decidual tissue. In the present series decidual tissue and chorionic villi in 30 cases of post-abortion endometrium with bleeding showed increased mast cells. These observations corroborated the findings of Mehra *et al*, (1970). This increase may be due to chronic inflammation, degeneration and necrosis which were associated with most of the cases. In cases with vesicular mole in metrorrhagia group, the average number of mast cells was found to be less, a finding similar to that of Saigal and Balasubrahmanyan (1963).

In the histologically normal myometrium from patients having normal menstrual cycle, the average mast cell count is quite high. They are more numerous in the fibrous connective tissue than in the muscle tissue. These findings are in agreement with those of Huguenin (1911); Staemmler (1921), Stieve (1929), Janes and McDonald (1948) and Fox and Abell (1965). The myometrium in adenomyosis in the metrorrhagia group showed less number of mast cells than that of fibroleiomyoma. In adenomyosis mast cells were more in the surrounding myometrium than in the endometrial tissue, but the stroma of the endometrial tissue associated with cystic hyperplasia and haemorrhage revealed more number of mast cells. This observation is in contradiction to the findings of Janes and McDonald (1948) and Saigal and Balasubrahmanyan (1963) for which no satisfactory explanation could be provided.

Fibroleiomyoma in the metrorrhagia group showed a good number of mast cells within the growth. But when compared with the normal myometrium the number was found to be low. This finding is similar to that of Fox and Abell (1963). In the present series, out of 25 leiomyomas studied, 10 had chronic inflammation, degeneration, necrosis and haemorrhage. In these cases mast cell number was quite high. The increase of mast cells in these cases can be attributed to these changes. More mast cells were observed in the subserous and submucous types than in the interstitial variety. The increased number of mast cells in these types may also be due to associated inflammation, degeneration and necrosis. It is known that the subserous type is more prone to degeneration and submucous type is more prone to infection and ulceration. In our series more mast cells were observed in the vicinity of the growth around the blood vessels, but the fibrous tissue of the growth proper showed less number of mast cells except in the surrounding areas of chronic inflammation, haemorrhage, degeneration and necrosis where the number of mast cells were more. These findings are in agreement with those of Fox and Abell (1965). Normal cervix from patients with normal menstrual cycle showed more mast cells than that of normal endometrium, but slightly less than that of nor-

mal myometrium. This finding corroborated that of Nozaka and Simpson (1962) and Fox and Abell (1965). Cervix from patients of metrorrhagia group with leiomyomatous polyp showed plenty of mast cells, particularly under the squamous epithelium and around the blood vessels. Most of these cases showed chronic inflammation also. These findings are in agreement with those of Staemmler (1921); Janes and McDonald (1948); and Saigal and Balasubrahmanyan (1963).

From an analysis of the above observations, it can be seen that there is definite increase of mast cells in the endometrium, myometrium and cervix in cases of abnormal uterine bleeding, such as menorrhagia and metrorrhagia. The increase of mast cell count in these various tissues is quite striking and it may be concluded that mast cells play a prominent role, probably through local release of heparin, which gets mixed with the menstrual blood and produce free and prolonged bleeding. Further studies including the assay of heparin in the discharged blood in uterine bleeding is necessary to confirm this view.

Summary and Conclusion

1. Mast cell distribution was studied in 370 cases. Of these 270 cases were of abnormal uterine bleeding and 100 cases with normal menstrual cycles as normal controls.

2. The average number of mast cells in the endometrium was found to be increased in both menorrhagia and metrorrhagia cases than in cases of menorrhagia.

3. Endometrial polyp and post-abortion endometrium revealed increased number of mast cells.

4. Endometrial tuberculosis and vesicular mole showed scanty mast cells.

5. Myometrium in adenomyosis and fibroleiomyoma, showed less mast cells. But fibroleiomyoma showed more mast cells than adenomyosis cases.

6. Increased number of mast cells were observed in cases with leiomyomatous polyp than in the normal cervix.

7. Distribution of mast cells in different tissues revealed increased mast cells, particularly around the blood vessels, surrounding areas of chronic inflammation, haemorrhage, degeneration and necrosis.

8. It is concluded that the increased number of mast cells in the uterus in cases of abnormal uterine bleeding may play a prominent role, probably through local release of heparin, which mixes with the menstrual blood and produce free and prolonged bleeding.

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References

1. Asplund, J. and Holmgren, H.: Acta. Anat. (Basel), **3**: 312, 1947.
2. Beber, B. A., Landing, B. H. and Sutherland, J. M.: A.M.A. Arch. Path., **69**: 531, 1960.
3. Fox, A. B. and Abell, M. R.: Amer. J. Obst. & Gynec., **91**: 433, 1965.
4. Harris, H. F.: Philad. Med. J., **5**: 757, 1900.
5. Huguenin, B.: Beitr. Geburtsh. Gynak., **16**: 324, 1911.
6. Janes, J. and McDonald, J. P.: Arch. Path., **45**: 622, 1948.
7. Latta, J. S. and Beber, C. R.: Science, **117**: 498, 1953.
8. Mehra, U., Devi, P. K., Chakrabarti, R. N. and Choudhury, R. R.: J. Obst. & Gynec. India, **20**: 792, 1970.
9. Nozaka, K. and Simpson, W. L.: Anat. Rec., **142**: 263, 1962.
10. Rumbolz, W. L. and Greene, E. G.: Am. J. Obst. & Gynec., **73**: 992, 1957.

11. Saigal, R. K. and Balasubrahamanyan, M. L.: J. Obst. & Gynec. India, 13: 542, 1963.
12. Staemmler, M.: Frankf. Ztschr. Pathol., 25: 391, 1921.
13. Stieve, H.: Zbl. Gynae., 53: 2706, 1929.
14. Tinel, J. and Vimuex, J.: C. R. Soc. Biol. (Paris), 146: 1915, 1952.
15. Vara, P.: Geburtsh. U. Frauenheilk, 22: 989, 1962.
16. Wislocki, G. B. and Dempsey, E. W.: Am. J. Anat., 83: 1, 1948.

See Figs. on Art Paper VI-VII