Original Article

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Status of Mast Cells in Autopsy Specimens of Prostate: A Cross-sectional Study

Pathology Section

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ABSTRACT

Introduction: Mast cells are found in areas rich in connective tissues and beneath epithelial surfaces. Mast cells have been extensively studied for their orchestration of allergic reactions and autoimmunity. Mast cells infiltrate various prostatic lesions in varying concentrations. Autopsy specimens had not been investigated extensively in the previous literature.

Aim: To find out a quantitative estimation of mast cells and the association of the number of mast cells in various prostatic lesions that included both inflammatory and neoplastic lesions in autopsy cases.

Materials and Methods: A cross-sectional, analytical study was carried out in the Department of Pathology, R.G. Kar Medical College and Hospital, Kolkata, India from April 2017 to March 2018. Sixty autopsy specimens of the prostate were dissected from the deceased males above 30 years of age. Four to six paraffin embedded sections from different lobes and peri-urethral areas were taken. Haematoxylin and Eosin (H&E) stained sections for histopathological diagnosis and toluidine-blue stain after water mounting to demonstrate mast cells by its metachromasia were performed. Mast cell densities were estimated by a light microscope under high power magnification (400X) on an average of 100 fields. Gross and microscopic findings were recorded. Data analysis correlation was done using Statistical Package for the Social Sciences (SPSS) software version 18.0. Mean and standard deviations were determined for different prostatic lesions. Group means were compared using the student's t-test. For statistical significance p-value of less than 0.05 was considered.

Results: A total of 60 autopsy specimens of the prostate were studied comprising 8 (13.5%) specimens of normal prostate, which acted as a control, 6 (10%) specimens of prostatitis, 27 (45%) specimens of Benign Hypertrophy of Prostate (BHP), 12 (20%) specimens of BHP with Prostatic Intraepithelial Neoplasia (PIN), 3 (5%) specimens of prostatitis with focal PIN and 4 (6.5%) specimens of prostatic adenocarcinoma. Mast Cell Density (MCD) was higher in prostatitis {6-8 per High Power Fields (HPF)}, compared to normal (1-3/HPF) and BHP (3-5/HPF), lowest in adenocarcinoma (1-2/HPF) and intermediate in PIN (2-4/HPF).

Conclusion: Mast cell density was the lowest in prostatic adenocarcinoma and significantly higher in prostatitis, probably due to a lack of antitumour immunity in higher grades, whereas it was significantly higher in chronic non specific prostatitis possibly because of inflammatory response.

Keywords: Benign hypertrophy of prostate, Hyperplasia, Intraepithelial neoplasia, Prostate cancer

INTRODUCTION

Mast cells are heavily granulated wandering cells that are found in areas rich in connective tissues beneath epithelial surfaces. Their granules contain heparin, histamine and many proteases. The heparin appears to play a role in granule formation. They have Immunoglobulin E (IgE) receptors on their cell membranes and like basophils, they degranulate when IgE-coated antigens bind to their surface. They are involved in anti-inflammatory responses initiated by immunoglobins IgE and IgG. The inflammation combats infection. Marked mast cell degranulation produces clinical manifestations of allergy upto and including anaphylaxis. Mast cells are plentiful in the anterior and posterior lobes of the pituitary gland. Masts cells are present in the fibrous capsule of the liver, along the blood vessels, beneath the mucosa of alimentary and respiratory tracts, prostatic tissues, and in other parts of the body. Each cell is round in shape and presents a central nucleus. The cytoplasm is closely packed with large membrane-bound granules, which stain metachromatically with toluidine blue, methylene blue, etc. Granules become purple-coloured when treated with toluidine blue. Histochemically the granules are produced by the sulfated mucopolysaccharides. Substances contained in the granules are heparin histamine, hexosaminidase, eosinophil and chemotactic factors.

Basic aniline dyes extracted from dahlia were first used to identify the mast cell. The mast cell granules were distinguished by giving a metachromatic staining reaction. The blue colour of the aniline dye is changed to red-violet by the replacement of histamine with amine molecules in the dye without morphological change [1].

Gupta RK first reported the presence of mast cells around Prostatic Carcinoma (PC) [2]. Many studies also reported mast cell aggregations at the periphery of PC as a significant prognostic factor. Moreover, the antitumour effect of mast cells had been postulated by many authors probably related to Tumour Necrosis Factor (TNF) and non TNF cytotoxicity. The majority of studies involving mast cells in human cancers remain correlative. Inflammatory cells are increasingly recognised to play a key role in the tumour micro environment in many human cancers. Mast cells have been extensively studied for their orchestration of allergic reactions and autoimmunity. Mast cells infiltrate various prostatic lesions in varying concentrations [3].

Mast cell infiltration is often observed around human tumours. Inflammatory cells such as macrophages, neutrophils and mast cells infiltrating around tumours are known to contribute to tumour growth; however, the clinical significance of mast cell invasion in Prostate Cancer (PC) has not been investigated extensively. The significance of mast cell infiltration around prostatic tumours has not been well studied, even though the accumulation of mast cells around the tumour was first reported more than a decade ago [2]. The study showed the distribution of mast cells varies in routine prostatic biopsies. Utilisation of mast cell count to separate benign from atypical and malignant lesions requires further evaluation because only a few studies are there in the literature. Although animal

studies were carried out in canine prostate biopsies, this study was the first of its kind in eastern India after searching extensively in the literature [4].

Stawerski P et al., studied prostate cancer with mast cell density and infiltration of mast cells suggested the promoter function of mast cells in prostate cancer formation and development, whereas no evidence was found for their opposite activity. A significant increase in mast cells is seen in benign prostatic hyperplasia [5]. Hempel Sullivan H et al., in their work based on the infiltration of mast cells and density of microvessels in prostatic carcinoma performed mast cell subtyping and reported a higher minimum number of the tryptase-only (MCT) subset of extratumoural mast cells is associated with an increased risk of biochemical recurrence [6].

The aim of the present study was to find out a quantitative estimation of mast cells and the association of the number of mast cells in various prostatic lesions that included both inflammatory and neoplastic lesions in autopsy cases.

MATERIALS AND METHODS

A cross-sectional, analytical study was carried out in the Department of Pathology, R.G. Kar Medical College and Hospital, and attached police morgue, Kolkata, India. Ethical approval was obtained from the Institutional Ethical Committee (No. RKC/6024). Informed written consent was taken from the relatives of the deceased and the study was initiated.

Sample size calculation: Considering 20% inclusion of autopsy cases for this study with 10% absolute precision and 95% confidence level using the formula= $z^2 \times p(1-p)/d^2$ sample size of 60 was obtained. Due to some medicolegal reasons, prostates from all deceased males above the age of 30 years could not be collected.

Inclusion criteria: Autopsy specimens of the prostate were dissected from the deceased male persons above 30 years of age, passed away less than 12 hours at the Police Morgue attached to R.G. Kar Medical College and Hospital, Kolkata, India were included in the study.

Exclusion criteria: Autopsy specimens of the prostate from deceased male persons less than 30 years of age and cases more than 12 hours of death were excluded from the study.

Study Procedure

At the time of autopsy the specimens of the prostate gland were examined thoroughly to find out any pathological lesions grossly. The collected glands were fixed in 10% formalin. The gross descriptions like size, shape, weight, surface, dimension, cut surface, etc. were noted. Attached organs like seminal vesicles, vas deferens, and lymph nodes including the urethra, if present were examined. Photographs of the specimen were taken. After gross examination, the prostate gland was serially sectioned in a plane perpendicular to the urethra at 3-5 mm intervals using a scalpel blade. Cut surfaces were examined. Two surgical margins including bladder neck surgical margin (one bit) and another urethral (apical) surgical margin (1-2 bits) were taken carefully during grossing. Sections from the apparently abnormal sites were taken. Routine paraffin-embedded sections were prepared for microscopic examination by H&E stain. The slides thus prepared were examined to detect the pathological lesion. For mast cell identification, deparaffinised sections were rapidly stained by 1% toluidine blue. The count of mast cells was principally done under a light microscope by identifying their metachromasia and was done manually in 10 different fields of each section at a high magnification of 400X. After examination, the result was analysed according to the World Health Organisation (WHO) tumour classification of prostatic neoplasms and the Gleason system of grading prostatic adenocarcinomas [7].

Study parameters

- History from the relatives of the deceased regarding any relevant information such as the clinical history of urinary hesitancy or urgency, Prostate-Specific Antigen (PSA) level, or previous Transurethral Resection of the Prostate (TURP). However, due to medicolegal issues detailed history could not be elicited from the relatives of the deceased in all the cases.
- Gross and microscopic examination of the specimens.
- Evaluation of number of mast cell infiltration (mast cell density) in the prostatic tissues.

Assessment of mast cells: Freshly stained toluidine blue sections were used for immediate observation of mast cells. Only mast cells with apparent cytoplasmic granules and an obvious nucleus were counted. Microscopic foci of metachromatic granules without nuclei were excluded. Sections were observed under a binocular light microscope (Olympus CH20i). Mast cells were detected by identifying their deep purple metachromatic granules and counted manually in each high power field at 400X magnification by using a 10X eyepiece and 40X high power objective. MCs were counted in consecutive High Power Fields (HPF) in each anatomical zone starting from one end and proceeding along the entire length of the section to the other end. The maximum number of high power fields that could be accommodated in each zone was counted. The counting of MCs was performed by two independent observers to minimise subjectivity. They recorded the findings of the same slides to reduce interobserver bias. The interobserver reliability was 81% with a kappa value of 0.9 signifying a strong level of agreement.

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 18.0. Mean, and standard deviations were determined for different prostatic lesions. Group means were compared using the student's t-test. For statistical significance p-value of less than 0.05 was considered.

RESULTS

A total of 60 autopsy specimens of the prostate were studied. Among these, eight (13.5%) specimens were of normal prostate with age ranging from 30-47 years and mean age of 40.7 years, which acted as controls. Six (10%) specimens of prostatitis (age ranging from 36-50 years and mean age of 44 years), twenty-seven (45%) specimens of BHP (age ranging from 42-58 years, mean age of 51.1 years), twelve (20%) specimens of BHP with a PIN (age ranging from 48-68 years, mean 57 years), three (5%) specimens of prostatitis with a focal PIN (age ranging from 52-70 years, mean age of 63 years), four (6.5%) specimens of prostatic adenocarcinoma (age ranging from 68-87 years, mean age of 75 years) [Table/Fig-1]. The mean age of carcinoma in prostate cases was 75 years ranging from 68-87 years. The mean age of BHP cases was 57 years ranging from 42-58 years.

Final diagnosis	n (%)	Age range (Years)	Mean age (Years)
Normal	8 (13.5)	30-47	40.7
Prostatitis	6 (10)	36-50	44
BHP*	27 (45)	42-58	51.1
BHP with PIN*	12 (20)	48-68	57
Prostatitis with focal PIN	3 (5)	52-70	63
Prostatic adenocarcinoma	4 (6.5)	68-87	75

[Table/Fig-1]: Age range of various prostatic lesions.
BHP: Benign hypertrophy of prostate; PIN: Prostatic intraepithelial neoplasia

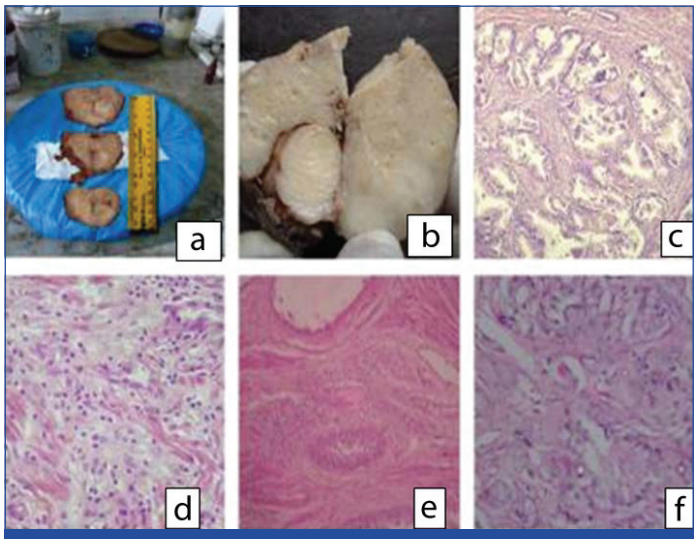
Among all types of prostatic lesions, prostatitis showed the highest number of mast cell infiltration in and around glandular and ductal areas of the prostate with mean±Standard Deviation (SD) of MCD

was 7±2.99 [Table/Fig-2]. The median lobe of the prostate is the common area for the occurrence of BPH. In the present study, it was found that 27 specimens of prostates (45%) had the features of BPH. Among the total of 27 BPH specimens,14 specimens showed mast cell accumulation (MCD-4/HPF, mean), detected by toluidine blue stain. Grossly BPH as a multilobulated surface, with variably sized nodules typically located around the prostatic urethra with the increased weight of the gland (40 grams average) [Table/Fig-3a,b].

The study revealed that mast cell infiltration occurs in BHP in 14 (51.8%) cases, which is lesser than in prostatitis (n=5, 83.5%), but higher than PIN or prostatic adenocarcinoma i.e., 1 (25%) case as shown in [Table/Fig-3c-f].

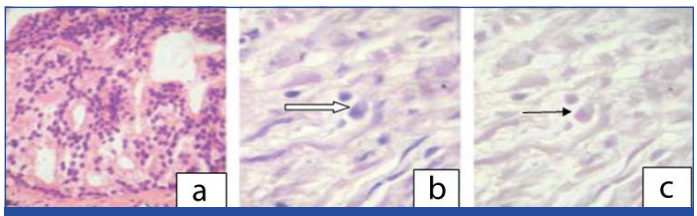
Final diagnosis	n (%)	Positive TB stain n (%)	MCD (Cells/ HPF)	MCD (Cells/ HPF) (Mean±SD)	Unpaired t-test	p-value
Normal	8 (13.5)	3 (37.5)	1-3	2±1.39	-	-
Prostatitis (non-specific)	6 (10)	5 (83.5)	6-8	7±2.99	-4.27	0.001
BHP*	27 (45)	14 (51.8)	3-5	4±2.09	1.67	0.104
BHP with PIN*	12 (20)	5 (41.7)	2-4	3±1.60	-0.719	0.481
Prostatitis with PIN	3 (5)	2 (66.6)	3-5	4±2.65	-1.9	0.09
Prostatic adenocarcinoma	4 (6.5)	1 (25)	1-2	1±0.50	-0.684	0.51

[Table/Fig-2]: Distribution of prostatic lesions (n=60) and comparison between normal and various prostatic lesions in respect of mast cell infiltration.
BHP: Benign hypertrophy of prostate; PIN: Prostatic intraepithelial neoplasia; TB: Toluidine blue; MCD: Mean cell density; HPF: High power fields; SD: Standard deviation

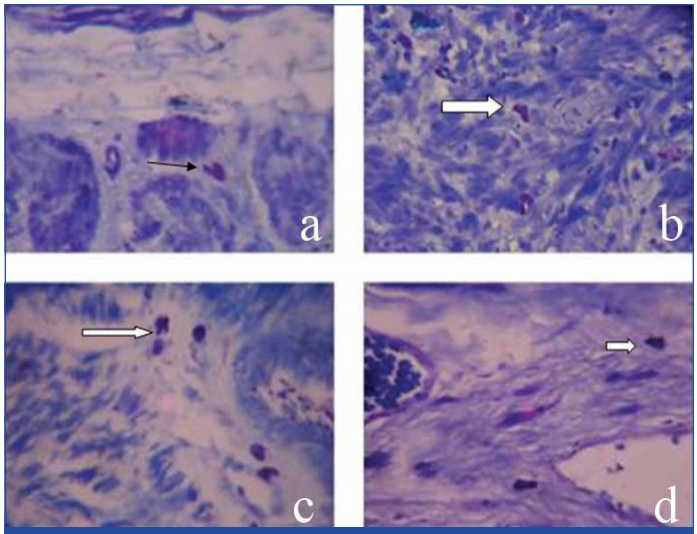


[Table/Fig-3]: a) Gross outer surface of prostatic adenocarcinoma involving the peripheral lobe-the cut surface of malignant growth; b) Benign hyperplasia of prostate fibromuscular glandular hypertrophy of prostate, benign prostatic hyperplasia, Glandular hyperplasia with increased MCD in the area of stromal hyperplasia (H&E stain,400X); c,d) BHP, Glandular hyperplasia with increased MCD in area of stromal hyperplasia (H&E stain,400X); e) Prostatitis stroma is infiltrated with chronic inflammatory cells (100X); f) Prostatic adenocarcinoma- atypical cribriform glands infiltrating prostatic stroma Gleason grade 8 (H&E stain, 400X).

Through the present study, authors have found 12 (20%) specimens of BHP with PIN and 3 (5%) specimens of prostatitis with PIN. MC infiltrations in BHP with PIN were seen in 5 (41.7%) specimens whereas, in prostatitis with focal PIN, it was in two out of three cases (66.6%). So mast cell infiltration is seen to be intermediate grade in PIN (highest in prostatitis and lowest in malignancy) as shown in [Table/Fig-4]. The present study demonstrated a total of four cases of prostatic adenocarcinoma with a Gleason Score of six and seven. The present study showed that it was lowest in poorly differentiated adenocarcinoma of the Prostate and significantly higher in Prostatitis [Table/Fig-5]. MCD was significantly higher in chronic non specific prostatitis. MCD in chronic non specific prostatitis was seven, which was significantly high in comparison to MCD one in prostatic adenocarcinoma. Mast cells were clearly seen under a light microscope as round, oval, or spindle shaped mononuclear cells with round to oval nuclei staining metachromatically a bright purple-red with toluidine blue [Table/Fig-5a-d].



[Table/Fig-4]: a) BHP with PIN II (H&E), x400; b) Mast cells (arrow) in PIN. H&E (400X); c) Mast cells (arrow) in PIN. Toluidine blue (TB) (400X).



[Table/Fig-5]: a) Prostatic adenocarcinoma toluidine blue (400X); b) Benign hyperplasia of prostate mast cells (shown by arrow) in area of stromal hyperplasia (H&E, 400X); c) Mast cells show red-purple colour with toluidine blue stain in prostatitis stained with toluidine blue (400X); d) Mast cells with toluidine blue stain in prostatitis stained with toluidine blue (400X).

DISCUSSION

The mast cell is a mystifying cell type whose pathophysiological function has engaged researchers for decades. These cells have been incriminated in diverse conditions, both inflammatory and tumoural. A predominance of MC has been found in various inflammatory and neoplastic disorders of prostate glands by several investigators who suggested that MC could be implicated in the pathogenesis of these lesions. However, the significance of MC infiltration around prostatic tumours had not been well studied, even though the accumulation of MC around tumours was first reported decades ago by Dimitriadou V and Koutsilieris M [8].

Talukder SI et al., studied surgical specimens of the prostate in a government-approved laboratory in the town of Mymensingh, Bangladesh, and observed different patterns of the disease [9]. The present study showed the occurrence of benign hyperplasia of the prostate (BHP) is 45%, whereas the study by Talukder SI et al., recorded an incidence of 77.4% BHP in their series which may be due to a large number of cases compared to the present study [9].

The present study showed that MCD is reduced to a minimum in poorly differentiated adenocarcinoma of the prostate and significantly higher in prostatitis presumably because of the paucity of antitumour immunity in the higher grade malignant tumours. Poorly differentiated tumours may lack antitumour response, which is associated with its invasive character and may explain the decreased MCD. In the present study, the occurrence of mast cell infiltrations in prostatitis appeared to be higher than lesions of the prostate with BHP. Infiltration of mast cells was significantly higher in prostatitis (p-value=0.001) probably due to antiinflammatory responses of mast cells. Deng WB et al, while studying the distribution profile of mast cells in benign and malignant prostatic lesions didn't observe any significant relations of mast cell distributions with inflammation [10]. 10% of cases in the present study

showed specific prostatitis. MCD in such lesions is observed to be between 6-8/HPF (mean being 7 HPF). Apart from Deng WB et al., who observed that there is no significant relationship between mast cell distribution and infiltration in BHP, other authors have concentrated on neoplastic lesions of the prostate only. In contrast to the present study, Amir T et al., observed mast cell count was significantly lower in inflammatory lesions (p-value <0.0001) [11]. This could have been probably due to degranulation of the mast cells.

Of the 12 cases of BHP with prostatic intraepithelial neoplasia (PIN), only 5 cases (41.7%) showed mast cell density (MCD) of 2 to 4/HPF. The rest of the seven cases failed to demonstrate mast cell infiltration in spite of extensive search through examination of multiple sections. The occurrence of mast cell infiltration in PIN had not been an area of interest amongst most of the authors as the studies were made on cases of carcinoma of the prostate [11]. Inspite of the examination of several sections in the remaining seven cases of PIN where mast cell could not be demonstrated, more blocks may have had to be studied in greater detail for a comment. Of the three cases of prostatitis with PIN, mast cell infiltrations were 3-5/HPF as shown in [Table/Fig-2]. Hence, it can point out that MCD is mildly higher in prostatitis (3-5/HPF) with PIN compared to (2 to 4/HPF) BHP with PIN, which may be due to the element of inflammation in such lesions.

Fleischmann A et al., studied the Immunological microenvironment in prostate cancer: high mast cell densities are associated with favourable tumour characteristics and good prognosis. This observation suggests the immune defense mechanism of mast cells in prostatic cancer. Stimulation of mast cells may be considered for immunotherapeutic treatment strategies in prostatic carcinoma [12]. Globa T et al., studied most cell phenotypes in benign and malignant tumours of the prostate and observed that the mast cell heterogenicity of phenotype is utilised as a promising therapeutic target in cancer treatment [13].

The count of mast cell infiltration was seen to be lowest in prostatic adenocarcinoma due to some unknown mechanism. Gupta RK reported the presence of mast cells around prostatic carcinoma (PC) which was s similar to Nonomura N et al., Çandir Ö, Aydin OA et al., [2,14,15,16]. A higher Gleason score was associated with increased mast cell count in contrast to samples with a low Gleason score [14]. They identified mast cells as independent prognostic markers in PCA using large cohorts of untreated patients with a long follow-up. Taverna G et al., also found mast cells as a potential prognostic marker in prostate cancer [17]. Johansson A and co-workers commented that peritumoural mast cell stimulates the expansion of human prostate tumour, whereas intratumoural mast cell negatively regulates angiogenesis and tumour growth and concluded that mast cells are novel independent prognostic markers in PCA and affect tumour progression [18].

The present study demonstrated a total of four cases of prostatic adenocarcinoma with a Gleason Score of 6 and 7. Among four specimens of prostatic adenocarcinoma, one specimen having mast cell infiltration of about 1/HPF was found [Table/Fig-5]. Amir T et al., observed mast cell profile in common prostatic lesions in their study [11]. They observed that absence or low count was the most significant finding in adenocarcinoma irrespective of the grade of the tumour with a concentration of mast cells around the tumour. Heparin, combined with a range of heparin-binding factors such as bFGF or TGF beta is able to promote neovascularisation and mast cell proteases causing cell structural alterations and the loss of the extracellular matrix integrity. Proangiogenic and antiangiogenic factors tightly regulate angiogenesis. Mast cell secretion stimulates angiogenesis through interacting pathways [19]. The role of mast cells in a tumour is rather controversial. They can have a poor antitumour effect depending on the tumour type and tumour microinvasion [17]. There is strong evidence that mast cells significantly influence angiogenesis and thus growth and progression in human cancers. Poorly differentiated carcinomas because of their invasive character may result in loss of antitumour response and therefore show scarcity of mast cells [20]. Probably by this mechanism, researchers have found the lowest mast cell infiltration in prostatic adenocarcinoma in comparison with normal or other prostatic lesions like prostatitis, BHP, PIN, etc.

Limitation(s)

Due to the limited number of cases available, the study sample size for calculating significance was rather small, which was reflected in the result. Further study with larger samples is required for more accurate findings. Furthermore, the method used for identifying mast cells was a simple one and better methods like ultrastructural study and immunohistochemistry could increase the accuracy of the findings.

CONCLUSION(S)

The present study showed that the count of mast cell infiltration is seen to be highest in prostatitis, lowest in malignancy and intermediate in PIN. A high mast cell density in the glandular element probably can be taken as an indicator that the lesion is not neoplastic. Poorly differentiated tumours may lack antitumour response, which is associated with its invasive character and may explain the decreased MCD. Therefore, MCD can be of value as a prognostic marker during the evaluation of prostatic biopsies. Also, stimulating mast cell activity might expand immunotherapeutic strategies in prostate cancer further study is required to explain the role of mast cells in tumour progression.

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