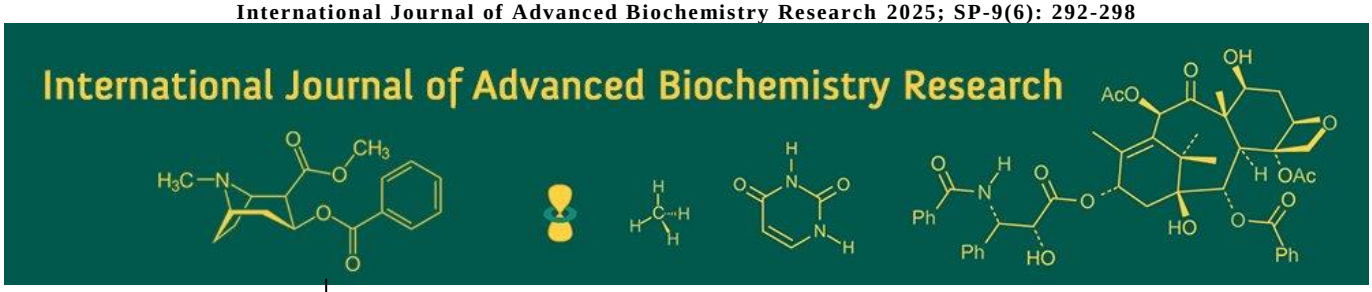

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Incidence and cytopathological evaluation of canine mast cell tumors

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Abstract
A canine mast cell tumor (MCT) is a common type of skin cancer in dogs that arises from mast cells, which are part of the immune system and play a role in allergic responses. These tumors can vary widely in appearance, from small, benign-looking lumps to large, ulcerated masses. They most frequently occur on the skin, but can also be found in internal organs. Diagnosis of canine mast cell tumors (MCTs) involves both identifying the tumor and determining its grade and potential to spread. The primary aim of the current study is to identify, incidence, occurrence and grading mast cell tumors of clinical samples submitted to Dept. of Veterinary Pathology. Veterinary College, Bengaluru. This study demonstrated relationship between Patnaik and Kiupel grading system and phenotypic traits, age and location of canine MCTs confirming the complex biological nature of this tumour.

Keywords: Canine, mast cell tumor, cytology, histopathology, grading

Introduction
Cancer accounts for between 14% and 27% of all canine deaths, making it one of the top causes of death in this species (Warland and Dobson, 2013) [18]. Since better pet care currently extends their life expectancy and makes it possible to diagnose late-life diseases like cancer, the number of tumors diagnosed is steadily increasing (Villamil *et al*., 2011; Grüntzig *et al*., 2015 and Śmiech *et al*., 2019) [17, 3, 12]. Skin tumors are among the most often diagnosed tumors, and mast cell tumors (MCTs) account for from 7% to 21% of all tumors (Welle *et al*., 2008; Grüntzig *et al*., 2015) [19, 3]. According to Blackwood *et al*. (2012) [1], MCTs might appear as solitary, tiny, single cases or as growing in multiple directions. Additionally, they can exhibit a broad clinical course of action by infiltrating nearby tissues and spreading to internal organs and the lymphatic system (Welle *et al*., 2008; Blackwood *et al*., 2012 and Śmiech *et al*., 2018) [19, 1, 12]. Much work is being done to determine the variables that may affect how this illness develops in the future (Warland and Dobson, 2013 and Śmiech *et al*., 2019) [18,12]. Histological grade is one of the most significant tumor predictors that might influence a tumor's morphological features, prognosis, responsiveness to treatment, and propensity for metastasis (Wu *et al*., 2006) [20].
On cytology, mast cells are round cells with a round to oval nucleus and a moderate amount of cytoplasm. The cytoplasm contains a variable number of granules that stain metachromatically and have a dark pink to purple colour (Kiupel and Camus, 2019) [5]. In mast cells with numerous granules, the visibility of the nucleus can be impaired (Kiupel, 2017) [6]. Often, granules of ruptured mast cells can be noticed in the background of the cytological slide (Johnson and Myers, 2017) [4].
Prior to 2011, the most commonly used MCTs histological grading system was the three-grade Patnaik system which recognizes three different categories: grade I, II, and III (Patnaik *et al*., 1984 and Śmiech *et al*., 2017) [10, 12]. According to Śmiech *et al*. (2017) [12] and Tamlin *et al*. (2020) [15], grade I tumors are well-differentiated and typically arise in the dermis, with subcutaneous tissue developing less frequently. These tumors seldom spread, do not infiltrate neighbouring tissues, and typically do not return following surgical excision with clean margins (Tamlin *et al*., 2020) [15]. They have a 100% chance of surviving for 12 months and a consistently favorable long-term prognosis (Tamlin *et al*., 2020) [15].

Compared to grade I, grade II, or intermediate grade, tumors have a greater propensity to spread to other areas of the body, infiltrate nearby tissue, and penetrate deeper layers of the epidermis (Tamlin *et al*., 2020) [15].

These tumors are more likely to return if they are surgically excised with limited margins or not totally. The 12-month survival rate for these malignancies is between 87% and 92% (Tamlin *et al*., 2020) [15]. According to Tamlin *et al*. (2020) [15], grade III or high grade tumors are highly aggressive, poorly differentiated, and have a 55%–95% metastasis rate. They also infiltrate deeply into the skin and underlying tissue. have a poor long-term prognosis with a 16%–46% chance of surviving for 12 months, necessitating extensive therapeutic care (Tamlin *et al*., 2020).

It can be challenging to forecast animal outcomes using grade II MCTs (Sabattini *et al*., 2015) [10]. These lesions can occasionally exhibit grade I tumor behavior or, more aggressively, grade III behavior (Sabattini *et al*., 2015) [10].

A new two-grade categorization system based solely on the shape of the cell nucleus and the number of mitotic figures was proposed by Kiupel *et al*. (2011) in response to these issues with behavior variability and uncertain clinical course. High-grade tumors occur less frequently, from 11% to 41%, while low-grade tumors occur more frequently, typically between 59% and 89% (Tamlin *et al*., 2020) [15]. High-grade tumors behave more aggressively, are more likely to spread and recur, and have a shorter survival period. The median survival duration for high-grade MCTs is approximately 4 months (12-month survival probability of 24%), while the median survival time for low-grade MCTs is over 2 years (12-month survival probability of 95%) (Kiupel *et al*., 2011) [7].

It has previously been shown that the age, sex, and body weight of castrated or sterilized dogs with MCTs are related (Shoop *et al*., 2015 and Grüntzig *et al*., 2016) [11, 3]. Despite the fact that MCTs are present in every part of the body, a number of studies proposed a possible prognostic relevance for multiple locations, such as the scrotum, inguinal, perianal, and mucocutaneous intersections (Welle *et al*., 2008 and Blackwood *et al*., 2012) [19, 1]. According to one study, the anatomical position of the tumor may be associated with a better or poorer prognosis (Pizzoni *et al*., 2018) [9]. However, MCTs are commonly observed on the head and neck (10%), limbs (25%–40%), and trunk (50%–60%) (Welle *et al*., 2008) [1]. Although MCT development in dogs can occur at any age, most cases are identified in dogs between the ages of 7.5 and 9 (Welle *et al*., 2008) [1].

Numerous studies have shown a breed-related predisposition to certain cutaneous tumors. Nevertheless, the relationship between breed and clinical aspects of disease is not sufficiently explored. The aim of this study was to conduct an epidemiological analysis of the risk of dogs having MCT graded by the Patnaik's and Kiupel's classification in comparison to other skin tumors, taking into account the dog's breed, age, sex, and tumor's anatomical location.

Materials and Methods

The current study conducted over the course of nine months, 90 suspected cases of spontaneously occurring skin tumor samples from Veterinary College Bengaluru's Hospital and other government hospitals in and around Bengaluru were submitted to the Department of Veterinary Pathology for cytopathological diagnosis.

The history and clinical signs shown by the affected animals were documented, together with their breed, age, sex, and location of occurrence. Additionally, the gross features of the tumors, such as their size, shape, color, consistency, ulceration, hemorrhage and inflammatory alterations, were also recorded. All the cases were revised and subclassified according with at least one of the following classifications systems: the three-grade malignancy scale of Patnaik *et al.* (1984) [8] and the two-grade malignancy scale of Kiupel *et al.* (2011) [7]. With the clinicopathological data collected, age groups were distinguished. Additionally, three broad anatomical locations were established: (1) head and neck, (2) trunk, (3) limbs.

Cytology

Fine Needle Aspiration Cytology (FNAC)

After fixing the affected mass between the fingers, 22" gauze fine needles were inserted into the tumor mass in various directions, and few cells were taken out. On dry, clean glass slides, the gathered tissues were spread into smears and stained with Giemsa stain.

The smears prepared for cytological examination were first checked for the quality of staining and cellularity. The morphology of cells, nuclear and cytoplasmic details were considered to diagnose neoplasia of mast cell tumors.

The cytological evaluation of mast cells consisted of the following parameters: mast cell granularity, anisocytosis, anisokaryosis, pleomorphism and karyomegaly, number of mitotic figures, number of binuclear mast cells and number of multinuclear mast cells.

Histopathology and classification

Representative tissue samples were immediately preserved in 10 per cent neutral buffered formalin and subjected to standard paraffin embedding procedures. Using a rotating microtome, sections with a thickness of 4 µm were cut. The Haematoxylin and Eosin technique was used to stain the chopped sections. These tissue sections were analysed in order to investigate and categorize the mast cell tumors under a microscope.

The canine mast cell tumours were classified according to the diagnostic criteria proposed by Patnaik *et al.* (1984) [8 and Kiupel *et al*. (2011) [7].

Ethical approval

All of the investigated samples were obtained for diagnostic purposes as part of routine and standard care. The researchers solely used the information derived from the cytological and histopathological diagnosis and had no control over how any clinical procedures were carried out.

Results

In the present study, 90 cases of spontaneously occurring skin tumors were collected and diagnosed. In these, 40 cases were cytologically and histologically classified as mast cell tumors**.**

Age

The age of occurrence of mast cell tumors ranged from 3 to 15 years, with an average mean age of 9.03 years. The highest incidence (30 %) of mast cell tumors were observed in the age group of 10 to 12 years, followed by 25 per cent in 8 to 10 years, 15 per cent in 6 to 8 years and 12 to 14 years, 7.5 per cent in 4 to 6 years and 5 per cent in 14 to 16 years. Only one case of MCT were observed in dogs aged 2 to 4 years (Table- 1).

Table 1: Age wise incidence of canine mast cell tumors

Age Group (years)	Incidence	Incidence Rate (%)
2 to 4	1	2.5
4 to 6	3	7.5
6 to 8	6	15
8 to 10	10	25
10 to 12	12	30
12 to 14	6	15
14 to 16	2	5
Total	**40**	**100**

Breed

Analysis of breed wise incidence of mast cell tumor showed highest incidence was reported in non-descript breeds with an incidence rate of 40 per cent followed by Golden Retriever (22.5 %), Labrador Retriever (15 %), German Shepherd, Boxer and Pomeranian (5 % each), Beagle, Shih Tzu and Pug each constituting 2.5 per cent (Table- 2).

Table 2: Breed wise susceptibility of mast cell tumors

Breed	Incidence	Per cent Incidence
Non-descript	16	40
Golden Retriever	9	22.5
Labrador Retriever	6	15
German Shepherd	2	5
Pomeranian	2	5
Boxer	2	5
Beagle	1	2.5
Pug	1	2.5
Shih Tzu	1	2.5
Total	40	100

Sex

In the current study, mast cell tumors were recorded in 57.5 per cent in male dogs and 42.5 per cent in female dogs (Table- 3).

Table 3: Sex wise occurrence of mast cell tumors

Sex	No. of dogs	Per cent Incidence
Male	23	57.5
Female	17	42.5

Location wise occurrence

In the present study, the trunk region showed significant site of occurrence, comprising 25 tumors, representing 62.50 percent of the total incidence. Meanwhile, the limbs region demonstrated involvement in 12 tumors out of 40, accounting for 30 percent of the incidence and 3 tumors were found in head and neck region accounting for 7.5 per cent (Table-4).

Table 4: Location wise distribution of canine mast cell tumors

Sl. No.	Region	Incidence	Per cent Incidence
1	Head and Neck	3	7.5
2	Trunk	25	62.5
3	Limbs	12	30.0
	Total	40	100

Gross pathology

In the current study among 40 cases, 28 cases were seen as a solitary nodule and 12 cases were seen as multiple nodules. Grossly, the size of the tumors varied from 2.5 to 20.0 cm at their greatest diameter. The growths were raised, firm, well circumscribed and adherent. They presented as either single, firm, well-defined growths or multiple nodular, firm, ulcerated well-defined masses (Fig 1). Some appeared as showing single, firm**,** erythematous tumor mass. some as a nodular, soft, lipoma like growth, some as single firm bleeding mass, few were seen as a single growth with firm, raised and well circumscribed alopectic mass, multiple nodular, firm ulcerative mass. Cut surfaces of the tumor showing creamy white or pinkish in color (Fig 2) and some cut sections reveal white with cellular surface, multifocal areas showed haemorrhages.

Cytology

Out of 90 FNAC (fine needle aspiration cytology) samples received, 40 samples were cytologically classified as mast cell tumours. Cytologic examination revealed large number of round cells having round to oval unstained nucleus with abundant pale cytoplasm containing numerous coarse, round, fine and purple granules. At times, the granules were seen obscuring the nucleus.

The cells appeared round or oval-shaped, with spherical, oval, or irregular nuclei, often eccentrically placed. Moderate to marked pleomorphism and anisokaryosis were observed (Fig 3). Nuclei displayed coarse chromatin with prominent single or multiple nucleoli (Fig 4) in some cells. A high nucleus to cytoplasmic ratio was evident, with varying degrees of cytoplasmic basophilia and in some multiple bizarre shaped nuclei and giant nuclei were observed.

Cytologically, well granulated mast cell tumor with poorly defined nuclear structure. moderately granulated mast cell tumor and poorly granulated mast cell tumor with well-defined nuclear structure and budding nuclei.

Histopathology

Out of 90 tumor tissue samples received, 40 samples were histopathologically classified as mast cell tumours.

Microscopic examination revealed round to polygonal having central to slightly eccentric nucleus with moderate amount of pale cytoplasm containing light grey to blue granules. The neoplastic cells were arranged in the rows and columns and few times ribbon like pattern were observed. In addition, abundant eosinophils were seen in between the neoplastic mast cells.

Special staining with toluidine blue characteristically stained the metachromatic granules in the cytoplasm of mast cells having round to polygonal nucleus (Fig 6).

Microscopically, the neoplastic mast cells were found infiltrating the stromal collagenous tissue and muscle fibres separating them along with a large number of eosinophils, which varied in numbers with the degree of differentiation of the tumor (Fig 5). The occurrence of mast cell tumor was mainly observed in dermis with infiltration of mast cells around sebaceous glands, blood vessels and lymph vessels. In well differentiated tumors the number of eosinophils was higher and was lesser in moderate to poorly differentiated types. In some, there was also presence of oedema, necrosis, haemorrhage, collagenolysis, infiltration of polymorphonuclear cells and ulceration of superficial skin epidermal covering. Eosinophils were commonly observed aggregating around foci of collagenolysis and in between the tumor cells.

The canine mast cell tumors were graded according to Patnaik *et al*. (1984) and Kiupel *et al*. (2011) system's histologic grading into well differentiated tumors (Grade I),

intermediately differentiated tumors (Grade II) and poorly differentiated tumors (Grade III) and High and Low grade respectively.

According to patnaik histopathological grading, among the 40 mast cell tumors, 14 (35.0 %) cases were well differentiated tumors (Grade I), 23 (57.5 %) cases were intermediately differentiated tumors (Grade II) and 3 (7.5 %) were poorly differentiated tumors (Grade III). According to kiupel histopathological grading, among the 40 mast cell tumors 33 (82.5%) were low grade tumors and 7(17.5%) were high grade tumors.

Grading

Patnaik grading of mast cell tumors (Table 5).

Well differentiated tumors (Grade I)

In the current study, 14 cases of well differentiated tumor cases were noticed. Microscopically, well-differentiated mast cells were arranged in rows or small groups, separated by mature collagen fibers of the dermis. Cells were round and monomorphic with ample cytoplasm; most had distinct cytoplasmic boundaries and medium-sized, intracytoplasmic granules. Nuclei were round with condensed chromatin. Mitotic cells were absent. There was minimal edema and necrosis in the neoplasms (Fig 7).

Intermediately differentiated tumors (Grade II)

In the present study, 23 cases of intermediately differentiated tumor cases were observed. These tumors were moderately to highly cellular, and the neoplastic cells infiltrated the lower dermal and subcutaneous tissue. Moderately pleomorphic cells were arranged in groups with thin, fibrovascular stroma, the neoplastic cells were round to ovoid and there were scattered spindle and giant cells. Most cells had distinct cytoplasm with fine, intracytoplasmic granules; however, the cytoplasm in some was indistinct and the granules were large and hyperchromatic. Nuclei were round to indented with scattered chromatin and single nucleoli; occasional cells had double nuclei were present. Mitotic cells were rare. areas of diffuse edema and necrosis noticed (Fig 8).

Poorly differentiated tumors (Grade III)

In the present study the poorly differentiated tumors were seen in three cases. These neoplasms were cellular and pleomorphic, and neoplastic tissue replaced the subcutaneous and deep tissues. The pleomorphic, medium-sized, round, ovoid, or spindle shaped neoplastic cells were arranged in closely packed sheets. The cytoplasm was indistinct with fine, intracytoplasmic granules. The indented to round vesiculated nuclei had one or more prominent nucleoli. Binucleated cells were common. There were many giant cells and scattered multinucleated cells. Coarse chromatin cells and Mitotic figures were also observed, mitotic cells were ranging from 3 to 6 cells per oil immersion (Fig 9). Edema, hemorrhage, and necrosis were present.

Table 5: Patnaik (3 tier) grading of canine mast cell tumors (n=40)

Sl. No.	Patnaik grade	No. of cases	Percentage (Total)
1	Grade I	14	35
2	Grade II	23	57.5
3	Grade III	3	7.5
	Total	40	100

Kiupel grading of mast cell tumors (Table 6)

Low grade tumors

In the present study the low-grade tumors were seen in 33 cases. Microscopically, Well-differentiated, round, monomorphic neoplastic mast cells commonly are arranged in rows that separate collagen bundles and are surrounded by edematous stroma (Plate-41). Large numbers of eosinophils commonly are observed and aggregate around foci of collagenolysis (Fig 10)

High grade tumors

In the current study, seven cases of high-grade tumor cases were noticed. Microscopically, neoplastic mast cells with atleast 7 mitotic figures in 10 high power fields (HPFs) were observed. Few cases showed atleast 5 mitoses in a single field of vision. Marked variation in nuclear size and karyomegaly were observed. At least 3 bizarre nuclei per 10 HPFs were observed. At least 3 multinucleated giant cells with 3 or more nuclei in 10 HPFs There was numerous multinucleated neoplastic mast cells were present (Fig 11 & 12).

Table 6: Kiupel (2 tier) grading of canine mast cell tumors (n=40)

Sl. No.	Kiupel grade	No. of cases	Percentage (Total)
1	High	7	17.5
2	Low	33	82.5
	Total	40	100

Discussion

The current study was conducted to investigate the incidence, occurrence, cytological, histopathological features in spontaneously occurring mast cell tumors in canines. Occurrence of mast cell tumours with increase in the age was also reported by Patnaik *et al*. (1984) [8]; Blackwood *et al*. (2012) [1]; Shoop *et al*. (2015) [11]. The current findings of the study were similar to the findings of Strefezzi *et al*. (2003) [14] who reported that the old age increased the risk of mast cell tumor development.

The probable reason for higher occurrence of mast cell tumours in in non-descript dogs could be due to their increased population, preference as a pet, higher presentation to Govt. Veterinary Hospital due to lower treatment expense. Further, Bostock, (1986) [2] opined that the correlation between breed and incidence of mast cell tumours should be taken into account based on the total number of dogs in each breed in a locality.

The current finding on incidence of mast cell tumour predominance in male may be attributed to pet owner preference of male dogs in comparison with female dogs. However, there was neither gender predilection nor the effect of sex hormones on MCT development and survival was opined by Smiech *et al*. (2019) [12].

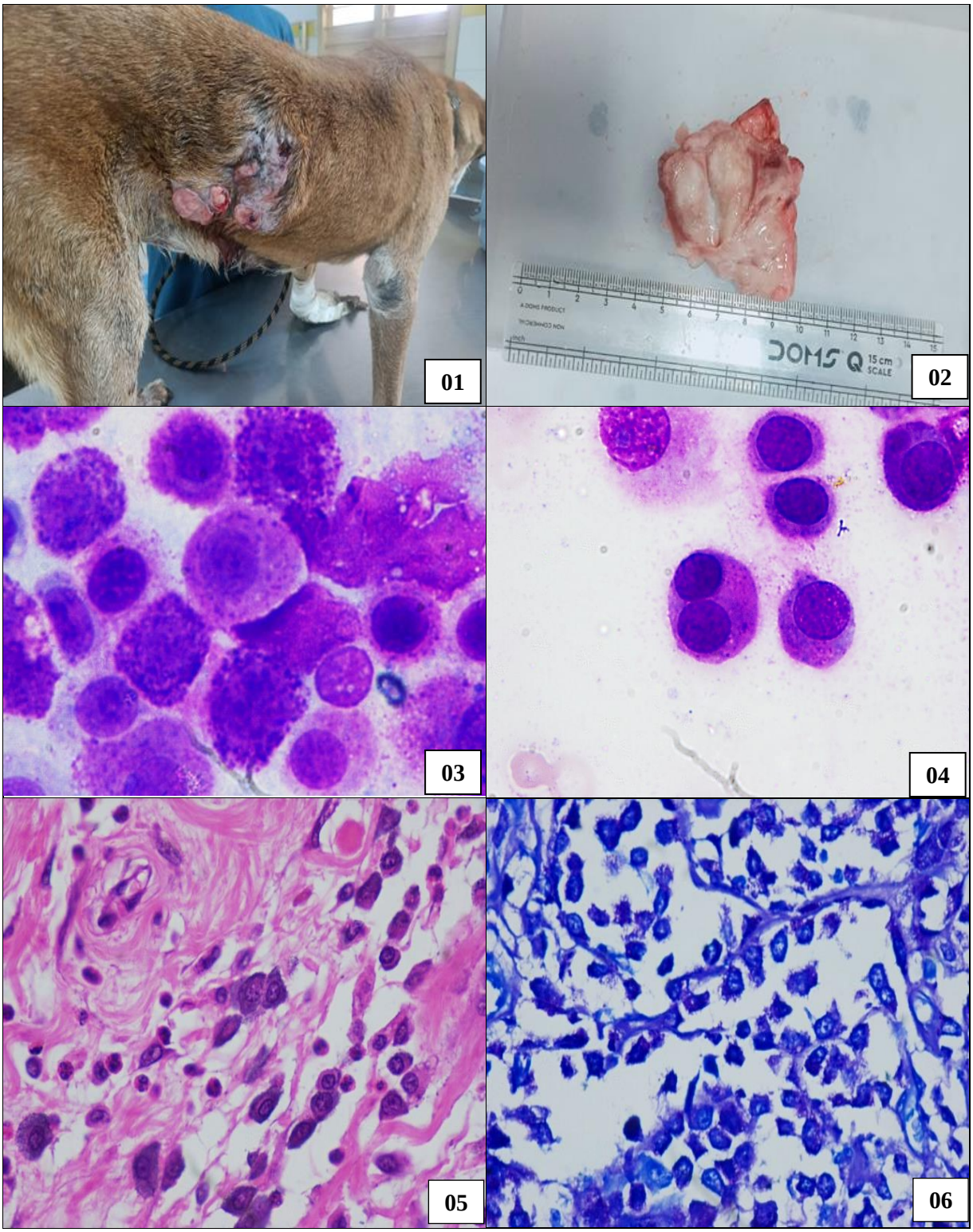
In the current study, the trunk region showed significant site of occurrence which was in accordance with the other studies of Welle *et al*. (2008) [19].

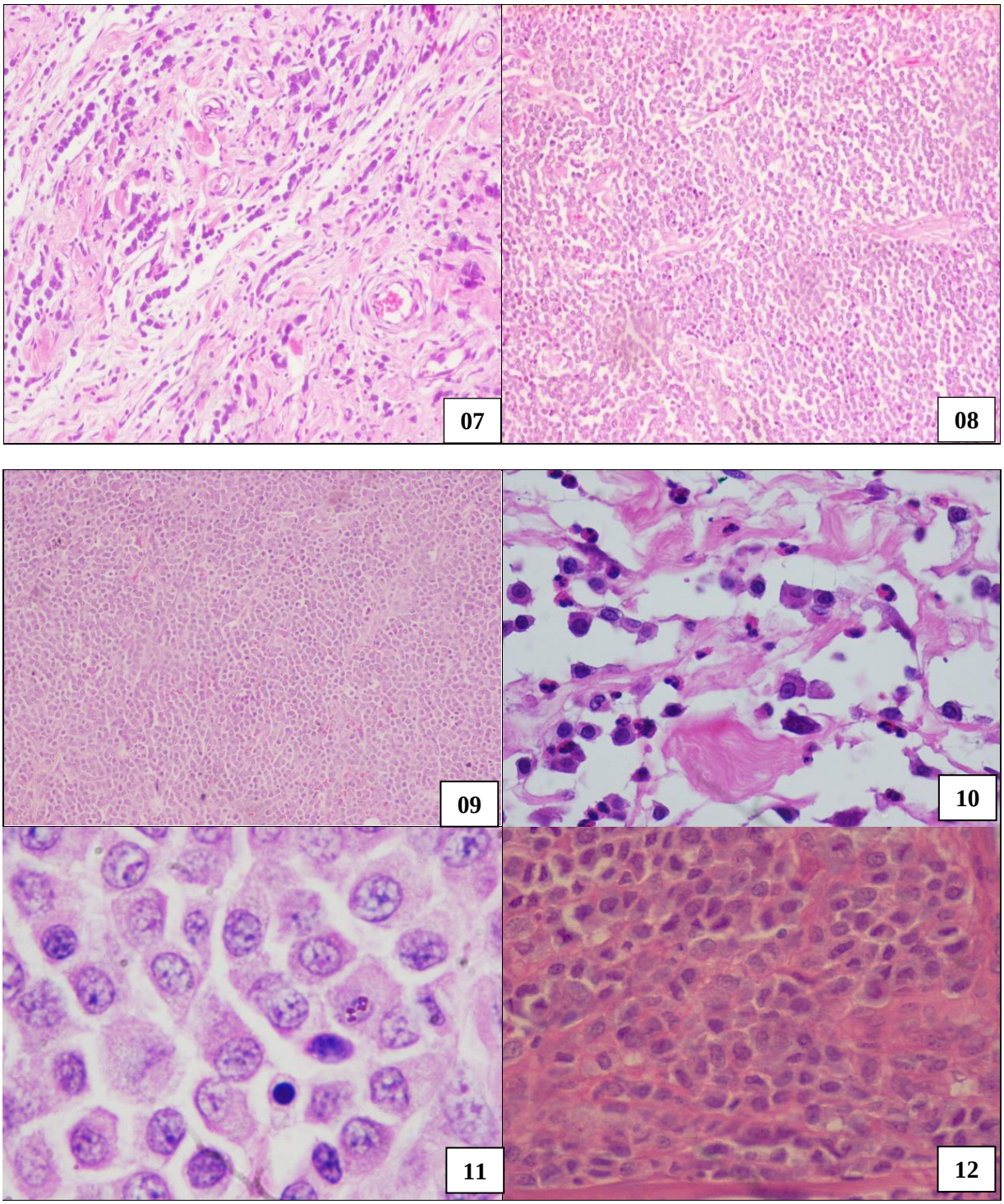
Cytologically, well granulated mast cell tumor with poorly defined nuclear structure. moderately granulated mast cell tumor and poorly granulated mast cell tumor with well defined nuclear structure. Similar cytological observations were also reported by Welle *et al*. (2008) [19]; Johnson and Myers, (2017); Kiupel, (2017) and Kiupel and Camus, (2019) [4, 6, 5].

On histopathological examination, Among the 40 mast cell tumors 14 (35.0 %) cases were well differentiated tumors

(Grade I), 23 (57.5 %) cases were intermediately differentiated tumors (Grade II) and 3 (7.5 %) were poorly differentiated tumors (Grade III) according to Patnaik system's histologic grading indicating a higher incidence of intermediately differentiated tumors (Grade II) which was also been reported by Patnaik *et al*. (1984); Bostock *et al***.** (1986) and Thamm *et al*. (2005) [8, 2, 16].

Another grading method by Kiupel, (2011) when applied to the current study of 40 mast cell tumors, 33 (82.5%) were low grade tumors and 7(17.5%) were high grade tumors on histological examination. This high incidence of low grade tumors reported in the present study was also observed by Kiupel *et al*, (2011); Blackwood *et al*. (2012) and Stefanello *et al*. (2015) [7, 1, 13].





1. Gross picture of mast cell tumor appearing as a multiple nodular, firm, well-defined ulcerated growths affecting the right abdominal region
2. The cut surface of mast cell tumor showing creamy white or pinkish in color
3. Cytological picture of mast cell tumor showing moderate to marked pleomorphism and anisokaryosis. Giemsa X1000
4. Cytological picture of mast cell tumor showing cells with prominent single or multiple nucleoli. Giemsa X1000
5. Histological section of mast cell tumor with neoplastic mast cells were found infiltrating the stromal collagenous tissue and muscle fibres separating them along with a large number of eosinophils. H&E X1000
6. Histological section of mast cell tumor with characteristically stained metachromatic granules in the cytoplasm of mast cells having round to polygonal nucleus. Toluidene blue X1000
7. Histological section of well-differentiated mast cells tumor with cells were arranged in rows, separated by mature collagen fibers of the dermis. Cells were round and monomorphic with ample cytoplasm; most had distinct cytoplasmic boundaries and medium-sized, intracytoplasmic granules H&E X100
8. Histological section of intermediately differentiated mast cell tumor with moderately cellular, pleomorphic cells were arranged in groups with thin, fibrovascular stroma and there were scattered spindle and giant cells. Most cells had distinct cytoplasm with fine, intracytoplasmic granules H&E X100

9. Histological section of poorly differentiated mast cell tumor with pleomorphic, highly cellular, neoplastic cells were arranged in closely packed sheets. The cytoplasm was indistinct with fine, intracytoplasmic granules. H&E X100
10. Histological section of low-grade mast cell tumor showing well-differentiated, round, monomorphic neoplastic mast cells commonly are arranged in rows that separate collagen bundles and are surrounded by edematous stroma. H&E X400
11. Histological section of high-grade mast cell tumor showing neoplastic mast cells with mitotic figures in high power field. H&E X400
12. Histological section of high-grade mast cell tumor showing marked variation in nuclear size and karyomegaly. H&E X400

Conclusions

In this investigation, there was brief account of occurrence and incidence of mast cell tumor in clinical specimens of in and around Bengaluru city. Giemsa stain proved optimal for highlighting cellular details, while toluidine blue stain effectively mast cell granules details in histological smears. Malignant tumours consistently manifested features such as hypercellularity, anisocytosis, anisokaryosis, the presence of mitotic figures, nuclear and nucleolar abnormalities, abnormal chromatin, and an elevated nuclear-cytoplasmic ratio. The study highlighted the use of both Patnaik and Kiupel grading system for effective diagnostic surveillance of mast cell tumor malignancy. Emphasizing the correlation between Patnaik and kiupel grading system, this research supports the routine incorporation of grading techniques as an adjunct for diagnosing mast cell tumor.

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