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# **REVIEW ARTICLE**

### Meckel's diverticulum in animals and birds: An immuno-pathoclinical perspective

# M. R. Gofur

Department of Veterinary and Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh

### Abstract

**Background:** Meckel's diverticulum (MD), also known as vitelline diverticulum, is a congenital anomaly found in animals and birds as an appendage of the small intestine with immunopathoclinical significance.

**Methods:** The author used PubMed and Medline search engines for articles containing terms such as Meckel's diverticulum, animals, birds, histopathology, complications and immune functions. From the abstracts of those articles, relevant articles were selected and reviewed them in detail. All the relevant major review articles and trials were included. The articles, which were available in full text English language, were selected. Additional articles were identified by a manual search of the references from the reviewed articles.

**Results:** MD is a vestigial remnant of the omphalomesenteric duct. MD is most commonly found in horses and swine and less common in ruminants, carnivores and aves. The gross morphology and location on small intestine varies species to species. Hereditary, breed, age and sex are the factors that influence the occurrence of MD in animals. Histologically the wall of the diverticulum is of the same construction as the small intestinal wall (mucosa, submucosa, muscular and serosa coats) with a few exceptions like lack of villi and has a large amount of aggregated lymphoid follicles in its tunica mucosae, and also its muscularis mucosae. MD is a novel lymphoepithelial organ in the birds because of its high amount of lymphoid tissue. It produces large number of plasma cells which are comparable to those of the gland of Harder. MD is not generally of great clinical importance, but it is occasionally involved in several patho-clinical complications like recurrent colic from impaction, the development of peritoneal adhesions and strangulations in animals.

### **Conclusion:**

The information included in the review regarding the development, prevalence, morphology, immunological and pathoclinical significance of Meckel's diverticulum is supportive to prevent complications which will result in morbidity and mortality in animals and birds.

Keywords: Diverticulum, small intestine, congenital anomaly, lymphoid tissue, plasma cells

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<sup>\*</sup>Correspondence: <u>royhangm@gmail.com</u>

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#### Introduction

Meckel's diverticulum, also known as vitelline diverticulum/ diverticulum vitellinum (Mc Lelland, 1990) or diverticulum caecum vitelli (Nickel et al., 1977) or diverticulum verum (Cohrs, 1966), is an uncommon embryonic developmental anomaly in human and animals representing persistence of the embryonic omphalomesenteric duct (also called the vitelline duct or yolk stalk), which is the embryonic connection between the primitive gut and yolk sac (Hooper 1989; Verwilghen et al., 2010; Huebner et al., 2013; Wong et al., 2017). Meckel's diverticulum was first described by Fabricius Hildanus in 1598 and later named (Meckel's diverticulum) by the German anatomist Johann Friedrich Meckel, who described the embryological and pathological features in 1809 (Meckel, 1809).

The vitelline duct is the embryonic communication between the yolk sac and the midgut by which the vitelline blood vessels enter the embryo (Branton et al., 1988). The duct is normally obliterated before the end of the first third of pregnancy (Jubb et al., 1993; Swenson, 1989). Incomplete closure and disappearance of the vitelline duct may result in a variety of abnormalities such as Meckel's diverticulum. vitelline cyst, persistent fibrous cord, umbilical sinus and umbilicoileal fistula (Grant and Tennat, 1973; Iwashita, 2006). Meckel's diverticulum from incomplete results obliteration and disappearance of the vitelline duct (near the ileum), and retained in postnatal life as a patent tube extending from antimesenteric side of the intestine to the umbilicus (Fig. 1) (Oshikata et al., 2015). The vitelline duct can be obliterated at both its ends and present one or more cysts along the corresponding tract (Riccaboni et al., 2000). Moreover, in chicken, the yolk duct continues to grow even after hatching for a period (Olah and Glick, 1984) and significant amount of yolk may pass through the yolk stalk into the intestine (Romanoff, 1960) and during its passage may be absorbed by the epithelial lining of MD (Kar, 1947). Occasionally an associated mesodiverticular band (vitelloumbilical band) may extend from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated (Fig. 2) (Jubb *et al.*, 1993; Verwilghen *et al.*, 2010; Smith, 2015).



Fig. 1. Meckel's diverticulum in the intestine of a White Leghorn chicken. Meckel's diverticulum, an important anatomical landmark in birds, is located at the junction between the jejunum and the ileum (https://partnersah.vet.cornell.edu/content/meckelsdive rticulum1).



Fig 2. Mesodiverticulur band extends from Meckel's diverticulum. A. Meckel's diverticulum with mesodiverticular band. B. One mechanism by which Meckel's diverticula can cause small bowel obstruction is entrapment of the intestine by a mesodiverticular band (Brunicardi *et al.*, 2009).

#### Development

The congenital anomalies of intestine in animals are rare in occurrence in comparison to other body organs (Jones et al., 1997; Singh and Parihar, 1997). Meckel's diverticulum is a remnant of the vitellointestinal duct (omphaloenteric, oomphalomesenteric) that communicates with the definitive yolk sac and the midgut in the four-week-old embryo. As the midgut grows during the fifth week the gut forms a U-shaped loop with the vitellointestinal duct at the apex. The duct divides the gut into cranial and

caudal portions. The cranial portion gives rise to the duodenum caudal to the entrance of the common bile duct, the jejunum, and the rostral two thirds of the ileum. The caudal half gives rise to the remaining portion of the ileum and the large bowel. During the sixth and seventh week of development the midgut undergoes elongation, partial rotation and herniates into an umbilical ceolom. While in the umbilical coelom, the vitellointestinal duct normally atrophies. During the tenth week of growth the midgut returns to the abdominal cavity. If there has been incomplete atrophy of the vitellointestinal duct by the time the midgut returns to the abdominal cavity, a Meckel's diverticulum results (Sprinkle et al., 1984; Jones et al., 1997).

On the other hand, the yolk sac is supplied by two vitelline arteries, one of which degenerates as the yolk sac atrophies, while the remaining artery develops into the superior mesenteric artery. When one of the vitelline arteries fails to degenerate, it develops into a peritoneum-covered fibrous band or a mesodiverticular band (Yoo *et al.*, 2003). It usually extends from the tip of the Meckel's diverticulum to the ileal mesentery.

### Prevalence

Meckel's diverticulum is observed between five and seven weeks of fetal life in humans. Normal omphalomesenteric channel should be closed in these weeks. MD results from the persistence omphalomesenteric duct (Bilici *et al.*, 2011; Huebner *et al.*, 2013). In human, Meckel's diverticulum occurs in about 2% of the population (Elsayes *et al.*, 2007). Prevalence in males is 3–5 times higher than in females (Moore *et al.*, 2013). Mostly found at young age, usually among children at the age of 2 (Schoenwolf and Larsen, 2009).

In domestic animals, Meckel's diverticulum is most commonly found in horses and swine (Grant and Tennat, 1973; Yeruham *et al.*, 2004; Wefel *et al.*, 2011; Barnes and Kelly, 2017) and rarely reported in cattle (Koch *et al.*, 1978; Erol *et al.*, 2014), dog (Marshall and Hayes, 1966), sheep (Cullen, 1916), chicken (Igbokwe and Abah, 2009, Udoumoh *et al.*, 2019), duck

(Mohammadpour, 2006; Abah, 2008; Gedam, et al., 2018), geese (Besoluk et al., 2002), guinea fowl (Abah, 2008), turkey (Barnes et al., 2000) and rat (Oshikata et al., 2015; Yamada and Inoue, 1992; Gupta 1973). Though, according to Nieberle and Cohrs (1967), MD present in 60% of the avian species, several authors found 100% in their studied birds like Gofur et al. (2009) in chicken, Mohammadpour (2006) in duck and Besoluk et al. (2002) in geese. MD is usually more prominent in the younger animals (Sprinkle et al., 1984; McLelland, 1975; Cohrs, 1966). Sprinkle et al. (1984) and Nieberle and Cohrs (1967) reported the familial or hereditary influence on the occurrence of a persistent divertictllum in animals. Meckel's Breed difference also differs on MD occurrence (Sprinkle et al., 1984). Although some authors (Nieberle and Cohrs, 1967; Grant and Tennat, 1973; Yeruham et al., 2004; Wefel et al., 2011) indicate that Meckel's diverticulum is a frequent finding in the horse and pigs. Sprinkle et al. (1984) and Singh (2007) claimed that the occurrence of MD is not frequent in horse and pigs, recpectively. Sprinkle et al. (1984) examined 15,000 horses postmortem at the University of Kentucky, Meckel's diverticulum was seen only in five horses (5/1500, 0.003%). In each instance, the diverticulum was a factor in the animal's death and not observed as an incidental finding. Singh (2007) screened for any gross abnormalities during routine inspection of 800 pigs at slaughter in Bareilly and Aligarh, Uttar Pradesh, India and found MD in only one (1/800, 0.001%) crossbred pig, aged about 6 months old and weighing 35 kg.

### Morphology

MD is generally a long tube of the same width (Cohrs, 1966) or slightly less width (Singh, 2007) than that of adjacent ileum in the pigs but in horses it is generally short conical or rounded sac of up to 10 cm diameter, which may be attached mesodiverticular folds to the ventral bv abdominal wall (Godlück 1967). Hahn (1877) described а large gastro-like Meckel's diverticulum with capacity of about 7 litres in a horse. A cord like appendage may be attached to its distal end. MD is usually single but

exceptionally there may be two on the ileum about 20 cm to 1 meter from the ileocaecocolic opening, on the wall opposite the mesenteric attachment in chicken (Cohrs, 1966). The shape, length and location of MD on the small intestine of different animals are presented in Table 1. MD was larger in size in local chicken than in the broiler (Igbokwe and Abah, 2009). The weight of MD in male is higher than that of female (Gofur *et al.*, 2009; Besoluk *et al.*, 2002) but Mohammadpour (2006) found no significant difference (p>0.05) on morphological factors (weight, thickness and length) of MD in between male and female ducks.

The contents of MD are those of the intestine (Cohrs, 1966; Gupta, 1973; Singh, 2007). Occasionally it has its own short mesentery in which the vitelline vessels open. MD was supplied both by one branch from the jejunal artery and by terminal branch from the cranial mesenteric artery and drained by cranial mesenteric vein (Besoluk and Eken, 2001).

Histologically though the wall of the diverticulum is of the same construction as the small intestinal wall (Cohrs, 1966; Jubb *et al.* 1993; Yeruham *et al.*, 2004; Singh, 2007; Oshikata *et al.*, 2015), there is presence of some distinct features in MD. The wall of MD consists of four histologically distinct layers: mucosa (comprised of lamina epithelia, lamina propria and lamina muscularis mucosa), submucosa, muscular and serosa coats. The outer serosa covers a thick layer of connective tissue, which may be corresponding to the sub-serosa of the intestine. Internal to this layer, bundles of smooth muscles are arranged around the MD. On the luminal side of the muscle, the connective tissue contains blood vessels and ganglions. This layer folds into the lumen of MD, and its surface is covered by columnar epithelium with mucous producing goblet cells. The proximal end of MD opens as a slit into small intestine on a flat, elongated papilla. Two longitudinal folds formed the submucosal connective tissue line the opening. These folds are covered by the intestinal epithelium (Yeruham *et al.*, 2004; Gofur *et al.*, 2018).

Compared with the jejunum or ileum, MD is lacking in villi, and has a large amount of aggregated lymphoid follicles in its tunica mucosae (in lamina propria and submucosa), and also its muscularis mucosae, which only had a circular layer, was very thin. A payer's patch often extends into it from the ileum (Cohrs, 1966; Besoluk et al., 2002; Mohammadpour, 2006; Igbokwe and Abah, 2009). Moreover, MD had a small number of crypts in the lumen. These features demonstrate that MD differs from digestive system particularly in its morphologic structure, and that it may play a functional role as a lymphoid organ. In the boundary between MD and the jejunum a circular sphincter is present, that was very thin, approximately 1.4 mm in diameter (in birds), constituted by the muscularis mucosae (Besoluk et al., 2002, Mohammadpour, 2006; Gofur et al., 2009; Igbokwe and Abah, 2009). However, Gupta (1973) documented a MD in a rat whose mucosal lining had villi lined with tall columnar epithelium similar to that present in ileum.

Parameter	Length	Location (anterior to the ileocecal junction)	Shape	References
Horse	12-15 cm	60-120 cm	Cone shaped or rounded	Cohrs, 1966; Sprinkle et al.,
	(about 10 cm in diameter)			1984; Jubb et al., 1993
Pig	5-30cm	-	Tube shaped	Jubb et al., 1993
Chicken	About 1.25 cm	20 cm to 1 meter	Comma or conical or	Cohrs, 1966; Getty, 1975;
			bean shaped	Igbokwe and Abah, 2009,
			-	Gofur et al., 2009
Duck	$6.92 \pm 0.89 \text{ mm}$	$61.84 \pm 5.64$ cm	Bean shaped or	Mohammadpour, 2006
			vermiform in appearance	-
Human	3-6 cm	60–100 cm	blind segment or small	Moore et al., 2013
			pouch like structure	
Rat	0.8 cm	14 cm	Saccular in appearance	Gupta, 1973

Table 1. Length, location and shape of Meckel's diverticulum in different species

#### Immunology

Meckel's diverticulum, a secondary lymphoid organ, is a member of gut-associated lymphoid tissue (GALT), and thus a part of gut/intestinal immune system. Nowadays MD regarded as the third pouch of the intestine (a third caecal pouch of the chicken (Maumus, 1902)) and a novel lymphoepithelial organ in the birds because of its high amount of lymphoid tissue (Oláh et al., 1984; Besoluk et al., 2002; Mohammadpour, 2006). In duck, it is a landmark that identifies the position of Payer's patches (McGarry and Bournes, 1980; Gedam et al., 2018). At hatching, no lymphoid tissue is found in MD; however during regression of the volk sac in the first two week after hatching myelopoietic tissue appears distal to the end of the diverticulum, whereas lymphopoietic tissue appears more proximal to the intestine, in the subepithelial connective tissue. After hatching, the epithelium growing into the subepithelial connective tissue from longitudinal folds, and beneath the epithelium, small groups of lymphoid cells accumulate (Schat et al., 2014). The lymphoid accumulation began about 2 weeks of age (Oláh et al., 1984; Mohammadpour, 2006; Teirlynck, 2009). The lymphoid tissue in the MD increases gradually with age and fills the folds. Concomitantly, the number of goblet cells is reduced; the epithelium is infiltrated bv lymphocytes, and inside the folds clusters of lymphoblasts are formed around the dendritic cells (Schat et al., 2014). Between 2 and 5 weeks of age the longitudinal folds were filled with lymphoid tissue. The intensive germinal center formation occurs between 5 and 7 weeks of age and large numbers of which are located close to the muscle layers (Olah et al., 1984; Jeurissen et al., 1988). Germinal center formation is associated with the

presence of secretory cells that means glandular structures are interposed amongst lymphoid follicles (Igbokwe and Abah, 2009). The absence of the secretory cells in the germinal centers followed by germinal center inactivity which is indicated by the lack of lymphoblasts and the high number of tingible body macrophages. The lymphoid tissue of MD seemed to be fully developed by 10 weeks of age and remained lymphoid at least until 21 months of age (Oláh et al., 1984). In its central region, lymphoid tissue is organized into primary and secondary lymphoid follicles, and interfollicular lymphoid cell accumulations (Fig. 3) (Casteleyn et al., 2010). Single CD45+ cells infiltrate the epithelium and connective tissue. Single B cells or plasma cells that are IgM or IgG or IgA+, also located in these infiltrates (Schat et al., 2014). The population of plasma cell subsets varies. There are more IgM positive cells followed by IgA and IgG positive cells in MD (Gofur et al., 2009). The main function of M-cells in lymphoepithelium with small rounded apical microvilli is capturing antigens from the gut lumen, processing and transferring them across the epithelial barrier to underlying immune cells, where occurs antigen presentation and initiation of the immune response (Burns and Maxwell, 1986). At a later age, both B and T cell areas can be distinguished. The T cell areas are adjacent the germinal center, whereas the B cell areas are generally beneath the epithelium (Jeurissen et al., 1988). In MD, the percentage of T and B -cells is 20 and 80%, respectively (El-Khayat, 2015). The function of MD is therefore double, and consists of nourishing the neonatal bird during the first days of life and acting as an immune organ in later stages.



Fig 3. Lymphoid tissue in Meckel's diverticulum. A. Lower magnification. Lymphoid tissue in Meckel's diverticulum (encircled) of a chicken. 1. Lumen of the jejunum, 2. Wall of the jejunum, 3. Meckel's diverticulum, 4. Adipose tissue; B. Higher magnification. 1. Lumen of Meckel's diverticulum, 2. Lymphoepithelium, 3. Aggregated lymphoid tissue, 4. Lymphoid follicle (http://www.histology-of-birds.com/galleries.php?id=63 and id=63&v=2).

Meckel's diverticulum produces large numbers of plasma cells which are comparable to Harderian gland and some of the novel gut-associated lymphoid tissue (GALT) like caecal tonsils, oesophageal tonsils, bursa of Fabricious and diffuse infiltrated areas of the cloaca whose role in immunological surveillance is being intensively studied (Gofur, 2020; Olah et al., 1984; Mohammadpour, 2006; Igbokwe and Abah, 2009). MD contains lymphoid follicles with profiles of lymphocytes, which are more abundant in broiler than in the local chicken (Igbokwe and Abah, 2009). There are more immunoglobulin-containing plasma cells in Meckel's diverticulum of female chickens than the male (Gofur et al., 2009).

#### **Clinico-pathology**

Usually the development of MD is asymptomatic and identified as an incidental finding during slaughter/necropsy of animals. But at times, it may be involved in several patho-clinical complications like hemorrhage, intestinal obstruction, diverticulitis, umbilical discharge, perforation, peritonitis and tumor, etc. (Fig. 4) causing abdominal pain (Houssin and Bussy, 2003; Singh, 2007; Gupta and Singh, 2011; Choi et al., 2017). Most common complications of MD are obstruction, diverticulitis and gastrointestinal bleeding. In humans, bleeding, obstruction, and diverticulitis are most commonly encountered (Cartanese et al., 2011; Erol et al., 2014). An mesodiverticular associated band may occasionally extend from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated (Smith, 2015). In horses, Meckel's diverticula and mesodiverticular bands are the most common types of congenital abnormalities that affect the small intestine (Southwood, 2008).

MD may undergo secondary dilatation as a result of impaction with masses of intestinal contents. When a collection of pus is present, the condition is termed empyema. When empyema becomes chronic, the exudate may undergo gelatinous mucoid change and produce the condition of hydropic dilatation. Bacterial decomposition of the contents may produce chronic inflammatory changes in the mucous membrane, with ulceration, gangrene and sometimes perforation followed by the fatal peritonitis or connective tissue thickening of the wall, local chronic peritonitis and formation of adhesions with neighboring organs. Extreme dilatation may lead to rupture (Cohrs, 1966; Sprinkle et al., 1984; Smith, 2015). MD also involved in volvulus, intussusception, obstruction and strangulation of the intestine (Sprinkle et al., 1984; Abutarbush et al., 2004; Erol et al., 2014; Maxie, 2016). Moreover, even in rat, MD may also become impacted with intestinal contents, ulcerate, become locally inflamed, and eventually perforate leading to abscess formation and peritonitis (Bertram et al., 1996). Sometime death of the animals is the ultimate fate due to these complications (Fig. 4) (Sprinkle et al., 1984).

There are various mechanisms by which MD can cause intestinal obstruction, such as: i) volvulus of small intestine around a fibrous band extending from Meckel's diverticulum to the umbilicus; ii) intussusception in which Meckel's diverticulum sags into the bowel lumen and then serves as a leading point to allow telescoping of the small intestine into first the distal ileum and then into the large intestine, causing ileoileal and ileocolic type of intussusception; iii) Littre's hernia, i.e. incarceration of the diverticulum in the hernia, causing intestinal obstruction; iv) entrapment of small bowel by the mesodiverticular band (Fig. 2B); v) stricture secondary to chronic diverticulitis; vi) Meckel's diverticulum lithiasis; vii) band extending between the diverticulum and the base of the mesentery, forming a loop in which a part of the ileum may get stuck, causing obstruction. Other mechanisms involve rare causes of obstruction like tumors, impacted meconium in neonates causing inflammatory adhesions of Meckel's diverticulum to surrounding structures leading to volvulus (Grant and Tenent, 1973; Sharma and Jain, 2008; Kuru et al., 2013; Savita et al., 2015).



Fig 4. Possible complications related to Meckel's diverticulum

MD is not generally of great clinical importance, but it is occasionally responsible for the conditions of clinically important. Clinical sign range from chronic colic pain for an impacted MD to acute severe colic if a mesodiverticular band strangulates intestine. This congenital disorder should be considered as a reason for abdominal pain and should be included in the differential diagnosis of acute abdominal pain and recurrent moderate colic in animals (Verwilghen *et al.*, 2010). The tentative diagnosis can be made by physical, clinical and ultrasound examinations, but correct diagnosis of MD before surgery is often difficult because a complicated form of this condition may be clinically indistinguishable from a variety of other intra-abdominal diseases such as inflammatory bowel disease, or other causes of small intestinal obstruction (You *et al.*, 2007) and treatment requires resection of the diverticulum and any associated bend (Smith, 2015). If a diverticulum is discovered during an exploratory laparotomy for reasons other than strangulation, one should consider the part of diverticulum sutured by bringing together and not creating penetration form of vertical lambert sewing technique to prevent strangulation in the

future. However, once strangulation occurs, prompt surgical treatment with resection and anastomosis of strangulated bowel may result in a favorable outcome (Erol *et al.*, 2014). Laparotomy with local anaesthesia at paralumbal region can be done for surgical resection of the diverticulum, as did by Erol *et al.* (2014) for a calf.

Meckel's diverticulum is also an important anatomical landmark in birds, as it is located at the junction between the jejunum and the ileum (Fig. 1) (Akers and Denbow, 2008, Hynd, 2019). Being able to differentiate the jejunum from the ileum is important to generating differentials for intestinal diseases. Some infections, such as coccidiosis, have a predilection for the jejunum and other diseases target the ileum; especially the *Eimeria acervulina* (one of the two most

pathogenic Eimeria sp.) reaches the jejunum in heavy infections. Lesions do not extend beyond Meckel's diverticulum (Al-Gawad et al., 2012; http://www.immucox.com/Coccidiosis/Diagnosis/ Site-of-Infection-for-Chickens). Petechial to ecchymotic haemorrhages may be present in the serosal surface of Meckel's diverticulum of fowl affected with highly pathogenic avian influenza (HPAI) virus (Swayne and Suarez, 2000). Abscess of the MD occur more frequently in poult with Poult enteritis complex (Barnes et al., 2000). Table 2 represents the pathological lesions in MD due to different diseases in birds. MD provides clinical signature for detection of different diseases in poultry and also help to avoid misdiagnosis of pathological disorders like polycystic immature teratoma in fowls (Besoluk et al., 2002; Igbokwe and Abah, 2009).

Table 2. Pathological lesions in Meckel's diverticulum due to different diseases in birds

Disease	Pathologic lesion	References
Avian influenza	Petechial to ecchymotic haemorrhages	Swayne and Suarez, 2000; Costa-Hurtado et al., 2015
Newcastle disease (Ranikhet disease)	Haemorrhage	https://ahd.maharashtra.gov.in/pdf/dis/Section% 20-% 20III.pdf
Tape worm infestation, Lymphoid leucosis, Coligranuloma (Hjarre's diseae)	Nodular thickening of the MD	https://ahd.maharashtra.gov.in/pdf/dis/Section% 20-%20III.pdf
Duck viral enteritis (Duck Plague)	Haemorrhage and contains a fibrinous core	Wobeser, 1997; Proctor et al., 1975
Toad venom toxicity	Dark necrotic lesions in MD	Gadelha et al., 2014

# Conclusion

Meckel's diverticulum, an uncommon congenital disorder, rarely occurs in animals and birds and sporadically involves in several patho-clinical complications causing abdominal pain and thus should be included in the differential diagnosis of acute abdominal pain and recurrent moderate colic in animals and polycystic immature teratoma in fowls. It provides nourishment the neonatal birds during the first days of life and acting as an immune organ in later stages. MD is a novel lymphoepithelial organ in the birds because of its high amount of lymphoid tissue (thus a member of GALT). Because it produces large number of plasma cells (thus comparable to Harderian gland, caecal tonsils, oesophageal tonsils etc.), its role in immunological surveillance is needed to be intensively studied.

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