CASE I: TP-10-016 (JPC 4019883).

Signalment: Five-year-old female cynomolgus macaque (Macaca fasicularis).

History: The animal presented with a clinical history of lethargy and anorexia. The neurologic examination revealed mild intention tremors, anisocoria, ataxia, and left-sided facial paralysis.

Gross Pathology: At necropsy, there was a tan to gray, granular, soft, irregularly-shaped mass that extended from the base of the skull at the level of the sella turcica, through the cribiform plate, to the upper areas of the nasal cavity and paranasal sinuses. The tumor compressed the ventral aspect of the brain from the frontal lobes to the midbrain.
Histopathologic Description: Slides from two different blocks of this tumor were submitted. This neoplasm infiltrated the nasal mucosa and propria submucosa, nasal septum (turbinate bone), flat bone (cribiform plate) and soft tissue/skeletal muscle. Sections of tongue, oral mucosa, and olfactory nerve were found in some but not all slides. This infiltrative and non-encapsulated mass was composed of neoplastic cells arranged in solid clusters, sheets, and lobules that were separated by delicate fibrovascular connective tissue. Tumor cells frequently formed true rosettes or pseudorosettes and had a primitive appearance. Neoplastic cells had small, round to polygonal, hyperchromatic nuclei and scant eosinophilic cytoplasm. Mitotic figures, as well as large foamy cells (nasal clear cells), and areas of hemorrhage and necrosis were commonly observed throughout the mass.

Multiple immunohistochemical (IHC) stains of this tumor were performed including ubiquitin carboxyl-terminal hydrolase L1 (PGP 9.5 neuron specific protein), CD56 (neuronal cell adhesion molecule), S-100, neuron specific enolase (NSE) and vimentin. The expression of PGP 9.5, CD56, S-100, NSE and vimentin, along with the gross and histopathologic findings, confirmed that this neoplasm was an olfactory neuroblastoma and ruled out other neoplasms such as malignant pituitary tumor, lymphosarcoma, meningioma, suprasellar germ cell tumor and intracranial schwannosarcoma.

Contributor’s Morphologic Diagnosis: Olfactory neuroblastoma.

Contributor’s Comment: Olfactory neuroblastomas are uncommon neuroectodermal tumors that may arise within the nasal cavity. The morphology of this neoplasm is heterogenous and the histogenic origin is unclear, resulting in many different names including, but not limited to, olfactory neuroblastoma, esthesioneuroblastoma, and olfactory neuroepithelioma. One paper describing a prospective study in humans suggests that the term "olfactory neuroblastoma" might be the most reflective of both the origin and nature of the neoplasm. This neoplasm has been described in humans, dogs, rats, cats, cows, a horse and a cynomolgus monkey. Interestingly, olfactory neuroblastomas are chemically induced in rats, as opposed to other animal species and humans where this tumor is typically of spontaneous origin. Some examples of chemicals that induce olfactory neuroblastomas in rats include 1-nitrosopiperazine and nitrosomorpholine. The development of olfactory neuroblastomas in rats is not related to the route of administration of the chemical but it is directly associated with chemical metabolism in nasal basal cells that leads to neoplastic transformation.

The differential diagnoses for this mass consisted of esthesioneuroblastoma (olfactory neuroblastoma), lymphosarcoma, suprasellar germ cell tumor, meningioma, intracranial...
schwannosarcoma, and malignant pituitary gland tumor. Since olfactory neuroblastomas originate from the olfactory epithelium, it is important to split the cranium along the midline into two sagittal half sections to locate the origin of the tumor in the nasal cavity with infiltration into the base of the cranial cavity.

This case was presented at the 2011 annual National Toxicology Program (NTP) Satellite Symposium, entitled *Pathology Potpourri* that was held in Denver, Colorado in advance of the Society of Toxicologic Pathology's 30th Annual Meeting, and published by Boorman G, et al. in the *Journal of Toxicologic Pathology*.2

**JPC Diagnosis:** Skull, nasal cavity and paranasal sinus: Olfactory neuroblastoma.

**Conference Comment:** Key histological features of this case include the arrangement of neoplastic cells into parallel arrays and the presence of pseudorosettes and occasional Homer-Wright type rosettes.5 Homer-Wright rosettes are composed of neoplastic cells surrounding a central lumen of fiber-rich neuropil. They are one of the major distinguishing characteristics of medulloblastomas, but also occur in primitive neuroectodermal tumors (PNETs) and pineoblastomas.10 Pseudorosettes, on the other hand, are formed by neoplastic cells palisading around a centrally placed vessel.10 Perivascular pseudorosettes are less specific than Homer-Wright rosettes in that they are also encountered in medulloblastomas, PNETs, central neurocytomas, glioblastomas and other tumors. Even with these characteristic lesions olfactory neuroblastomas can display a wide range of microscopic appearances with a large differential diagnosis. Immunohistochemically, these tumors are usually positive for some, or all, of the following: S-100 and neuroendocrine markers such as neuron-specific enolase (NSE), synaptophysin, chromagranin and CD56.5

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**References:**


**CASE II:** E 1242/12 (JPC 4033368).

**Signalment:** 1-day-old chickens (*Gallus gallus domesticus*), male and female.

**History:** Numerous one-day-old chickens in a hatchery were found in a weakened state.

**Gross Pathology:** Necropsy did not reveal any significant lesions.

**Laboratory Results:** ELISA yielded in the detection of antibodies against avian encephalomyelitis virus.

**Histopathologic Description:** Brain, longitudinal section (including cerebrum with brainstem and cerebellum): Multifocally, predominantly affecting large nuclei in the brainstem and the cerebellar Purkinje cells, there is neuronal degeneration characterized by marked dispersion of Nissl substance (central chromatolysis). Less commonly, neuronal necrosis is evident with neuronal hypereosinophilia, shrunken or swollen cell bodies, karyopyknosis, karyorrhexis and karyolysis.

With some slide variation, few neuronal cell bodies are surrounded by low numbers of astrocytes (satellitosis). Occasionally, macrophages phagocytosing cellular and karryorhectic debris (neuronophagia) as well as discrete nodules composed of low numbers of glial cells and fewer lymphocytes replacing neurons (glial nodules) can be observed. Scattered minimal to mild predominantly perivascular lymphocytic and histiocytic infiltrates (lymphohistiocytic cuffing) are present.

**Contributor’s Morphologic Diagnosis:** Brain: Neuronal degeneration and necrosis, mild to moderate, acute, multifocal with minimal satellitosis, neuronophagia glial nodules and minimal to mild, acute, multifocal, lymphohistiocytic encephalitis.

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2-1. Brain, 1-day-old chicken: Multifocally, and most visibly in the brainstem nuclei, neurons exhibit central chromatolysis, a characteristic finding in avian encephalomyelitis. (Photo courtesy of: Department of Veterinary Pathology, Freie Universität Berlin, Germany; http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/wel2/index.html)
**Contributor's Comment:** Avian encephalomyelitis (AE) was first reported in 1932 as a nervous disorder of chickens with pronounced and rapid tremor of the head and neck with, in some cases, ataxia. The symptoms worsened when the chickens were excited and disappeared in sleep. The causative agent, avian encephalomyelitis virus (AEV), belongs to the *Hepadovirus* genus of the *Picornaviridae* family and transmission occurs via the oral-fecal and vertical routes. Avian encephalomyelitis affects chickens, turkeys, and quails. Synonyms for AE include “infectious avian encephalomyelitis” and “epidemic tremor.”

Clinically, outbreaks occur in young birds, less than six (typically 1-3) weeks of age. The animals develop ataxia with possible progression to paralysis or tremor of the head and neck (i.e., epidemic tremor). In general, the severity of the disease depends on the age and immunological status of the bird. Whereas clinical signs might be present at the time of hatching, they are usually evident between 1-2 weeks of age. There seems to be a marked resistance if exposure is after 2-3 weeks of age. Adult birds show a drop in egg production for no more than two weeks.

Gross lesions are commonly absent, especially in adult chickens. Whitis areas in the ventriculus muscle due to massive lymphocytic infiltration may occur. Histologically, lesions may be lacking in the peracute stage. Typical lesions of acute AE include central chromatolysis of neurons in the brainstem (medulla oblongata) and of Purkinje cells. The neuronal nuclei isthmi, ruber, reticularis, rotundus and cerebellaris as well as the ventral horns of the spinal cord are primary targets. A disseminated lymphoplasmahistiocytic encephalomyelitis with ganglioneitits of the dorsal root ganglia can be detected in more subacute to chronic cases. In addition, nodular microgliosis, predominantly in the cerebellar molecular layer, may be observed. Multifocal microgliosis of the Purkinje cell layer, with triangular or flame-like extensions into the molecular layer are also suggestive of AE. Additionally, aggregates of lymphocytes appear within the muscular wall of the ventriculus, the pancreas and myocardium.

Differential diagnoses include Marek’s disease virus, which causes lymphoid infiltrates in the peripheral nerves and lymphomatosis of the viscera (not seen in AE), Newcastle disease virus, with peripheral chromatolysis rather than the central chromatolysis of AE, and Avian influenza virus.

**JPC Diagnosis:** Brainstem nuclei: Central chromatolysis, multifocal, mild.

**Conference Comment:** The contributor provides a thorough overview of avian encephalomyelitis virus. Clinical disease due to AE has also been described in pheasants, partridges and turkeys, though these species appear to be less susceptible than chickens.
The *Picornaviridae* family is composed of eight genera: *Aphthovirus*, *Enterovirus*, *Teschovirus*, *Cardiovirus*, *Erbovirus*, *Kobuvirus*, *Hepatovirus* and *Parechovirus*. Picornaviruses are non-enveloped, icosahedral, single stranded, RNA virions. Diseases of veterinary importance caused by picornaviruses include foot-and-mouth disease (*Aphthovirus*), encephalomyocarditis virus and Theiler’s mouse encephalomyelitis virus (*Cardiovirus*), swine vesicular disease (*Enterovirus*), porcine teschovirus 1 (*Teschovirus*) and avian encephalomyelitis virus. Originally classified in the genus *Enterovirus* and later reclassified into the genus *Hepatovirus*, AEV has recently been considered for classification into a new genus within the *Picornaviridae* family, *Tremovirus*.

The striking feature of this case is the paucity of microscopic lesions, consistent with the peracute disease course described in this case. Conference participants debated the presence of Purkinje cell degeneration and central chromatolysis, however a consensus was not reached. The hypercellularity of the submitted specimen also confounded uniform diagnosis in this case, as development of the brain is still ongoing in a 1-day-old chick, and differentiation of maturing, migrating, and developing cells of neural and glial origin from those associated with viral infection.

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**References:**

CASE III: UFSM-2 (JPC 4034401).

Signalment: 5-year-old female mixed-breed domestic pig (*Sus scrofa domesticus*).

History: A mixed-breed pig in good plane of nutrition and with no detectable clinical abnormalities was sent to slaughter. The federal meat inspector detected "areas of green discoloration in the carcass" and sent large tissue samples from several organs to be examined at our lab.

Gross Pathology: Grossly, over the ribs and beneath the parietal pleura there were green, smooth, and opaque, irregularly contoured, non-circumscribed, soft, homogenous areas. Light green masses that partially or completely obliterated the bone marrow architecture were observed at the cut surfaces of some ribs and several vertebrae and sternebrae. In all lumbosacral vertebrae, typically a subperiosteal presentation was observable. In the cut surface of long bones (femora and humeri), the same pattern of presentation was observed in the metaphysis. In the kidneys, there were multiple, 1-3 mm in diameter pink to light green, soft, irregularly shaped nodules. There was a homogeneous aspect to the cut surface of these nodules. At cut surfaces of popliteal and iliac lymph nodes, there were pink or light green areas. In one of the lymph nodes (internal iliac), the cut surface was diffusely light green and crisscrossed by red serpiginous lines.

Laboratory Results: Cytological examination of the mass revealed large numbers of round cells approximately 20-30 µm. These round cells had round, oval, or reniform nuclei that contained slightly clumped chromatin and did not display prominent nucleoli. The cytoplasm was scant, and a fine eosinophilic granularity could be observed in the cytoplasm of some neoplastic cells but not in others. Such cells were interpreted as myelocytes belonging to the eosinophil lineage.

Histopathologic Description: Histologically, a sheet of round cells with a virtually imperceptible stroma obliterated the bone marrow. The bone marrow tissue surrounding these cellular sheets was replaced by fibroblasts and collagen (myelofibrosis). At these sites, there was reabsorption of compact bone and moderate periosteal reaction. Non-circumscribed foci of myeloid cells were observed dissecting, and at times replacing, the renal tubules. Sections of these areas revealed that the neoplastic cell cytoplasm stained red by the Sirius red eosinophil technique and demonstrated strong cytoplasmic positivity for myeloperoxidase by the immunohistochemistry stain. All sections were negative for all the other immunohistochemical markers (lysozyme, CD 117, CD3 and CD79) used.¹

Contributor’s Morphologic Diagnosis: Bone marrow, vertebral body: eosinophilic granulocytic sarcoma.
Contributor’s Comment: Granulocytic sarcoma is a morphologic presentation of myeloid sarcoma, a hematopoietic neoplasm affecting bones or extramedullary sites; in this latter case, the growth is also referred to as extramedullary myeloid tumor, myeloblastoma, or myelosarcoma. Granulocytic sarcomas may originate from variably differentiated precursors, from both neutrophilic and eosinophilic lineages. Such sarcomas tend to occur grossly as characteristic green masses; therefore, the sobriquet "chloroma," derived from the Latin transliteration of the Greek khlorós, meaning green, was given to the neoplasm.

In humans, granulocytic sarcomas precede or occur concomitantly with acute myeloid leukemia, chronic myeloproliferative disorders, or myelodysplastic syndromes but are also described without association with any other hematologic disturbance. In the veterinary literature, granulocytic sarcomas are mentioned affecting dogs, cats, cattle, a rabbit, and a pig. In dogs and cats, the more consistently involved organs are the lungs, intestine, skin, lymph nodes and liver. In one of the few reports found in the veterinary literature, this tumor is mentioned as a mass in the neck of a Bull Terrier dog. In cattle, skeletal muscle is characteristically affected. In the case reported in a rabbit, the granulocytic sarcoma involved the skin, subcutaneous tissue, and skeletal muscle of the perineum. In the reported case in the pig, the tumor involved liver, kidneys, and mesenteric lymph nodes.

Differently from what occurs in human patients, animals affected by granulocytic sarcomas are almost always aleukemic; however, progression to a leukemia may occur. The current report describes gross findings, cytology, histopathology, histochemistry, and immunohistochemistry of a multicentric eosinophilic granulocytic sarcoma affecting a pig.

Granulocytic sarcoma was suspected in the current case based on the presence of light green masses in the gross inspection of the carcass and viscera, a typical aspect of this tumor. The anatomical distribution of the lesions observed in the current case is quite similar to that described for human granulocytic sarcomas, in which the occurrence is primarily subperiosteal and involves mainly the ribs, sternum, and pelvis. The microscopic presentation pattern observed both at cytological and histological examination consisting predominantly of precursor cells with myelocyte differentiation, allowed the presumptive diagnosis of well-differentiated granulocytic sarcoma. Immunohistochemistry results established the cell origin as of the granulocytic lineage, and histochemistry determined that the cells were possibly of eosinophil lineage, definitively confirming the diagnosis suspected at gross examination.

The definitive diagnosis of myeloid sarcomas is based on the association of phenotypic (cytology, histology, cytochemistry, and histochemistry) and Immunophenotypic (immunocytochemistry and...
immunohistochemistry) aspects. An immune phenotype of neoplastic cells positive for myeloperoxidase is the hallmark for granulocytic sarcoma. Other antibody markers have reportedly yielded positive results when applied to human cases of granulocytic sarcoma, including CD13, CD33, CD117, CD15, CD68, CD43, and lysozyme. However, lysozyme and CD68 are also marked in cases of monoblastic sarcoma, a less common form of myeloid sarcoma.

In the porcine tumor described here, the negative staining for CD117 could be explained by both the predominance of myelocytes and absence of myeloblasts, which are precursor cells that express this antigen. The negative staining for lysozyme was somewhat expected because swine granulocytes have been described as negative for this marker, whereas porcine monocytes and/or macrophages are strongly positive, similar to what is described in humans, a species in which lysozyme is the choice marker for monocytes and/or macrophages. Based on this species-specific feature, the negative reaction to lysozyme further helps to differentiate granulocytic sarcoma from monoblastic sarcoma.

In human patients, several different forms of lymphoma presentation are often confused with myeloid sarcoma and thus should be the main tumors to be included in the differential diagnosis. In the current case, the differentiation was made based on the following aspects: histological evidence of cytoplasmic eosinophilia, fine granularity observed in the cytoplasm of neoplastic cells when examined in cytological preparations, occurrence within the neoplasm of more mature eosinophil precursors amidst myeloblasts, and the immunohistochrometry results. Furthermore, the observation of light green masses that partially obliterated the bone marrow of several flat and long bones prompted the suspicion of granulocytic sarcoma, as this is the only hematopoietic neoplasm that expresses this typical color grossly. The green discoloration observed in fresh tissue specimens is due to the presence of myeloperoxidase and substantially helps in the diagnosis of granulocytic sarcoma.

Few lesions could grossly resemble granulocytic sarcoma. Such lesions include chlorellosis, a granulomatous algal infection observed in human beings and animals, and eosinophilic myositis, which is frequently associated with Sarcocystis spp. infection in cattle and has been described in a pig. The association of gross examination, cytology, histology, histochemistry, and immunohistochemistry findings is consistent with a diagnosis of eosinophilic granulocytic sarcoma.

**JPC Diagnosis:** Bone marrow, vertebral body: Eosinophilic granulocytic sarcoma.

**Conference Comment:** As noted in the comprehensive contributor’s comment, cytoplasmic myeloperoxidase positivity provides an immunohistochemical indication of the myeloid origin of granulocytic sarcoma, while the cytological characteristics, including the presence of reniform nuclei and faint eosinophilic cytoplasmic granules that stain with the Sirius red technique, specifically confirm eosinophilic lineage. Myeloperoxidase is a lysosomal enzyme found in myeloblasts, immature myeloid cells and the primary granules of mature neutrophils, while the Sirius red eosinophil technique stains eosinophilic cytoplasmic granules strongly red. McGavin and Zachary and Latimer provide detailed lists of specific leukocyte granules, however this is a rapidly developing field of research and there is substantial inter-species variation, so most lists of leukocyte granules are not all-inclusive. Conference participants had some difficulty in distinguishing eosinophilic cytoplasmic granules in this case, which was likely due to a loss of cytologic detail secondary to decalcification of these sections of bone.

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**References:**
CASE IV: H11-164 (JPC 4007419).

**Signalment:** 1-week-old male Charolais (*Bos taurus)*.

**History:** The calf had a history of hemorrhage from the rectum, injection sites and ear-tag site.

**Gross Pathology:** Carcass described by submitting veterinarian as markedly anaemic with widespread mucosal and serosal ecchymoses/petechiae and diffuse splenic congestion. Formalin-fixed sections of bone marrow from the sternum, femur and ribs were submitted for histopathological examination.

**Laboratory Results:** PCR on spleen for bovine pestivirus (bovine viral diarrhea virus – BVDV) was negative. No significant bacterial isolates from tissues.

**Histopathologic Description:** Sternebra: There is diffuse hypoplasia of all three marrow hematopoietic cell lines with less than 10% cellularity (i.e. hematopoietic tissue as a percentage of the total of hematopoietic and adipose tissue). Multifocal, variably-sized aggregates of myeloid and erythroid precursors; megakaryocytes are absent. Multifocally, adipocytes are separated by small areas of hemorrhage and by fine, fibrillar, eosinophilic material (gelatinous transformation).

**Contributor’s Morphologic Diagnosis:** Sternebral marrow: Trilineage hypoplasia of hematopoietic cells, severe.

**Contributor's Comment:** The trilineage hypoplasia in the bone marrow (aplastic pancytopenia) together with the clinical history, post-mortem findings, age of calf and the absence of BVDV are consistent with a diagnosis of bovine neonatal pancytopenia (BNP). This condition was first described in Germany in 2007 but has since been reported in many European countries. The condition is characterized by multiple (external and internal) hemorrhages, thrombocytopenia, leukopenia and bone marrow depletion in calves less than 4 weeks of age. It has been postulated that BNP occurs as a result of...
an isoimmune reaction mediated by maternal antibodies in colostrum. The occurrence of the disease has been linked to maternal vaccination with a particular BVDV vaccine, to such an extent that the European Commission suspended marketing of this vaccine in 2010. A vaccination history was not available for this animal.

Aplastic pancytopenia has historically been uncommon in cattle but has been documented in association with infection with BVDV type 2. BVDV type 1 has been isolated from cases of fatal hemorrhagic thrombocytopenia but experimental infection has failed to replicate the condition. Fatal hemorrhagic pancytopenia has also been reported in cattle due to ingestion of bracken fern and of T-2 mycotoxins.

**JPC Diagnosis:** Bone marrow, sternebra: Trilineage pancytopenia, diffuse, severe.

**Conference Comment:** A study examining the pathogenesis of BNP found that dams vaccinated with a particular BVDV vaccine produce alloreactive antibodies that cross react with the bovine kidney cell line used in vaccine production. These maternal autoantibodies, passed to their calves in colostrum, bind to leukocyte surface antigens, leading to opsonization, subsequent phagocytosis by macrophages and, ultimately, trilineage bone marrow hypoplasia.

Alloimmune phenomena are also described in several other species, including foals, humans and piglets. Neonatal isoerythrolysis (NI) in foals, a common alloimmune disease in foals, is a type II hypersensitivity reaction caused by the presence of anti-erythrocyte antibody complexes in the colostrum of the dam and results in destruction of erythrocytes. This condition occurs in horses because of exposure to an incompatible blood type from the stallion. NI has also been reported in cattle and cats. In neonatal alloimmune thrombocytopenia (NAIT), women homozygous for a certain genetic trait, who are carrying a fetus with heterozygous platelet antigens partially inherited from the father, may develop anti Human Platelet Antigen 1 antibodies. These antibodies pass through the placenta, causing fetal thrombocytopenia and subsequent intracranial hemorrhage.

*WSC 2013-2014*

4-2. Sternebra, marrow, 1-week-old calf: Higher magnification of metaphyseal marrow spaces – the marrow lacks erythropoietic cells of all lineages. (H&E 200X)
hemorrhage.\textsuperscript{1} NAIT has also been described in foals and piglets. In foals, it is hypothesized that the mare’s plasma and milk contains antibodies reactive to foal platelet antigens inherited from the sire.\textsuperscript{5} In contrast to BNP, which affects all hematopoietic cell lines, these conditions target one cell line; NI impacts erythrocytes while NAIT targets platelets, resulting in hemolytic anemia and thrombocytopenia respectively.\textsuperscript{1,5}

In general, viruses and toxins are the most common causes of pancytopenia. In addition to those infectious/toxic agents described by the contributor, further potential causes of pancytopenia include radiation, chemotherapeutic agents, estrogen toxicity, stachybotryotoxicosis, infectious agents and myelophthisis.\textsuperscript{10,11} Chemotherapy induced myelosuppression is the most common cause of canine pancytopenia, and is typically associated with doxorubicin administration.\textsuperscript{11} Estrogen compounds, which may originate from iatrogenic administration or hormone overproduction, are also myelotoxic. Disease is typically characterized by irreversible pancytopenia with widespread hemorrhage.\textsuperscript{10} Stachybotryotoxicosis is a pancytopenic disease of horses and ruminants that occurs due to ingestion of feed contaminated with the fungus \textit{Stachybotrys alternans}.\textsuperscript{10} Feline and canine parvoviruses target proliferating cells, such as epithelial cells within intestinal crypts or hematopoietic cells within the bone marrow, resulting in pancytopenia.\textsuperscript{10,12} Myelophthisis refers to replacement of normal hematopoietic bone marrow elements with abnormal tissue, usually neoplastic cells or fibrous connective tissue.\textsuperscript{6} Bone marrow neoplasia can be primary (multiple myeloma, leukemia, lymphoma) or metastatic.\textsuperscript{6} Malignant histiocytosis has also been associated with canine pancytopenia, likely due to a combination of decreased marrow production and cytophagia.\textsuperscript{12} Bone marrow fibrosis, or myelofibrosis, is most commonly reported in dogs, and may occur with sepsis, neoplasia, drug toxicity and immune-mediated disease.\textsuperscript{6}

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**References:**