

Comparative Pathology Case 18

Contributor : YS Ho (何逸僊), MD, MS

Associate Professor of Pathology, Chang Gung Medicial College, Taiwan

Clinical History : A 69-year-old male had chronic headache history for years, and aggravated in recent 2 days. Also, he is alcoholism with frequently presenting alcoholic withdraw syndrome. Brain CT showed a right temporal tip mass lesions, 9.5×9.0×8.0 cm in size, along sphenoid ridge with heterogenous enhancement and with extension across Sylvian fissure to frontal gyri inferiorly associated with severe perifocal edema. Angiography revealed a hypovascular mass with middle cerebral artery elevated upward. He received craniotomy with right temporal lobectomy, followed by four times of intrathecal MTX because of positive for tumor cells in CSF study and 1800 CGY irradiation therapy for the subinsular residual tumors. The patient is alive and well 5 months after the operation.

Diagnosis : Malignant lymphoma, diffuse large cell type and B cell in nature (on the base of the Working Formulation of Non-Hodgkin's Lymphoma for Clinical Usage)

Gross Findings : The tumor was yellowish in color, soft in consistency, and easily sucked.

Histopathological Findings : Histologically, the tumor was composed of sheets of monotonous neoplastic cells with an oval or round nucleus and scanty basophilic cytoplasm. Foci of necrosis was noted.

Immunocytochemical Results : LCA and L26 : diffuse positive. EMA, AE1/AE3, NSE, MT1, Vimentin, and HMB45 : negative.

Discussion : Lymphatic tissue is not normally found within the central nervous system, and primary malignant lymphoma of the brain (PMLB) is thought to originate from blood components. Immunosuppressive therapy, HIV infection, and many inherited and sporadically occurring immunodeficiency states are associated with an increased risk for lymphoma. Although secondary meningeal spread develops in a significant percentage of patients with high-grade systemic lymphoma, parenchymal involvement of the brain is rare. PMLB is uncommon and represents from 0.8 to 2 percent of all primary intracranial tumors; however, the sharply

increasing incidence of these tumor has been emphasized in recent reviews. PMLB lesions frequently involve deep structures, such as the basal ganglia, periventricular regions, and have indistinct borders. Most PMLB are aggressive B-cell neoplasms. T-cell neoplasm also have been recognized. Multifocal lesions is seen in as many as 50% of cases. The PMLB has a distinctive radiographic appearance with densely and diffusely enhancing after the administration of contrast material under CT or MRI examination. The prognosis of PMLB is known to be very poor compared with malignant lymphomas in other parts of the body, most reported patients have died within a year. However, in some reports showed that patients whose central nervous system lymphoma is not associated with systemic disease have a more favorable prognosis. and spontaneous regression was also found. The advatsages for the management of PMLB require rapid and more extact pathologic diagnosis, and patients suspected of PMLB should not be started on corticosteroid unless herniation is imminent., resection should be avoid, and chemotherapy should be initiated before the RT begins.

Differential Diagnosis :

1. Metastatic carcinoma
2. Melanoma.
3. Primitive neuroectodermal tumor.
4. Inflammatory pseudotumor.

Diagnostic Criteria : Small Blue Neoplastic cells with positive of Leucocyte common antigen & L26.

References :

- 1) Reyes CV. Primary malignant lymphoma of the brain in acquired immune deficiency syndrome (letter) . Acta Cytol 29 : 85-86, 1985
- 2) National Cancer Institute. Summary and description of a working formulation for clinical usage : the non-Hodgkin's lymphoma pathologic classification project. Cancer 49 : 2112- 2135, 1982.
- 3) Hochberg FH, Miller DC. Primary central nervous system lymphoma. J neurosurg 68 : 835- 853, 1988.
- 4) Jack CR, O'Neill B, Banks PM, Reese DF. Central nervous system lymphoma : histologic types and CT appearances. Radiology, 167 : 211-215, 1988.
- 5) DeAngelis LM. Primary central nervous system lymphoma : A new clinical challenge. Neurology 41 : 619-621, 1991.

6) 何逸僊：第 10 章：中樞神經系血液性疾病,腦腫瘤病理學 PP194-226 ,
華香園出版社, 台北. 台灣, 1995.

Immunohistochemical Results : Neoplastic cells exhibited positive reactions to antibodies of CD3, CD4, CD5, and CD8 demonstrated by the avidin-biotin peroxidase complex method ; however, they were negative to the antibody of Pan-B.

Electron Microscopic Findings : The nuclei of the neoplastic cells were irregular in shape and had abundant heterochromatin. There were only few short strands of rough endoplasmic reticulum in the cytoplasm, and few microvilli on cell surface. Cells containing small numbers of giant osmophilic granules similar to those undergoing apoptosis were seen scattered among neoplastic cells (Ozaki et al., 1994).

Discussion : The gross appearance of the tumor mass observed at the junction of cecum and ileum in the Wistar rat appears to be similar to the ileocecal immunocytoma noted in Lou/C/Ws1 rats. Nevertheless, the ileocecal immunocytoma is B cell in origin and type A viruslike particles have been demonstrated in the neoplastic cells (Burtonboy et al., 1978).

The starry-sky histologic feature observed in the present case appears to be identical to that described in human Burkitt's lymphoma.

In normal rats, mast cells are present in abundance in the mesenteric lymph nodes and tongue as well as a few in the thymus, liver, mammary gland, skin, digestive tract etc, and are rare in the lung, spleen, and adrenal. No mast cell is seen in the kidney, brain, spinal cord or eyes (Majeed, 1994). Nevertheless, mast cells were frequently seen in all of the organs affected by the lymphoma in our case; the unusual wide distribution and significant quantity of mast cells seen in the present case are of interesting.

For future study, it is worthwhile to investigate the relationship between mast cells and the T cell tumor by tumor cell culture and to identify possible growth factors, oncoproteins or lymphokines from tumor cells that may affect normal mast cell population and/or distribution. We have currently tried tumor transplantation to nude and SCID mice, and the results will be reported separately.

Diagnostic Criteria :

1. Histological identification : The tumor is composed principally of large lymphoblastic cells with high N/C ratio. The nuclei are round to ovoid, not indented or twisted, and usually surrounded by a moderate amount of cytoplasm with high mitotic index.

2. Histochemistry : Toluidine blue stain shows the presence of mast cells among the lymphoblastic neoplastic cells.
3. Immunohistochemistry : Neoplastic cells carry T cell markers.
4. Ultrastructural findings : Characteristic features of T cell origin (Cossman et al., 1978).

References :

1. Burtonboy, G., Berckers, A., Rodhain, J., Bazin, H. and Lamy, M. E. 1978. Rat ileocecal immunocytoma - An ultrastructural study with special attention to the presence of viral particles. J. Natl. Cancer Inst. 61:477-484.
2. Cossman, J., Deegan, M. J. and Schnitzer, B. 1978. Thymoma: an immunologic and electron microscopic study. Cancer 41:2183-2191.
3. Majeed, S.K. 1994. Mast cell distribution in rats. Arzneimittel-Forschung. 44:370-374.
4. Ozaki, K., Maeda, H., Nishikawa, T., Nishimura, M. and Narama, I. 1994. Chediak-Higashi Syndrome in rats: light and electron microscopical characterization of abnormal granules in Beige rats. J. Comp. Pathol. 110:369-379.

Comparative Pathology Case 20

Contributor : H Chiang (江宏), MD

Chairman, Department of Pathology, Veteran General Hospital

Clinical History: A 43-year-old Taiwanese aboriginal woman suffered from low back pain and weakness of both legs. A cisternal myelogram revealed multiple filling defects in the spinal canal from the lower cervical region to the caudal equina. Open biopsy of the spinal cord with excision of the cystic lesions were done. The patient's low back pain subsided and no further neurological deficit developed after operation.

Diagnosis: Sparganosis.

Gross Finding: There were glistening white and opaque organisms adhering to the distal spinal cord and lumbosacral nerve roots. They were 2 to 3 mm in diameter and appeared to be irregular cysts with branches and buds. The specimen submitted for pathologic examination were fragments of the excised cystic lesions measuring up to 0.3x0.5x0.7 cm in size.

Microscopic Findings: There were different shaped profiles of the larvae on the section. the body wall of the larvae consists of a tegument with microvilli. Bundles of longitudinal muscle were seen scattered throughout the parenchyma. The excretory canals were prominent and the calcareous corpuscles were evident in the loose paunchyma. The surfaces of the worms were clean without inflammatory exudate everywhere. There was no scolex identified.

Discussion: Sparganum, the generic term of the plerocercoid (second stage) larva of a pseudophyllidean tapeworm. The adult tape worm live in the intestine of dogs and cats. The species of tapeworms responsible for human sparganosis belong to genus Spirimetra. Cyclops is the first intermediate host of this tapeworm and fish, snakes, and amphibians are the second intermediate host.

Man becomes infected in 3 ways : (1) he may drink water containing an infected cyclops; (2) he may ingest a sparganum when he eats the flesh of a infected 2nd intermediate host; or (3) he may acquire the infection by apply the flesh of an infected 2nd intermediate host to an open wound.

The majority of patient have slowly growing subcutaneous nodules. Sparganosis may also develop in subconjunctival tissue, brain, spinal cord or virtually any place of the body.

There were two kinds of sparganum. The ordinary sparganum neither buds or branches. It is named sparganum mansonii or nonproliferative sparganum. It has been reported from most parts of the world including a few cases from Taiwan. Another kind of sparganum is called proliferative sparganum. It is caused by a rare form of sparganum in which the larvae reproduce in the intermediate by asexual continuous branching and budding. 3 cases have been reported in Taiwan previously.

Diagnostic Criteria: Diagnosis depends upon gross and microscopic identification of the sparganum. The stroma and tegument closely resembles that of the cysticercus and coenurus. The elongated worm-like configuration of a sparganum can usually be distinguished from the cystic configuration of a cysticercus or a coenurus. Cysticerci and coenuri have scolex with sucker and hooklets whereas sparganum do not.

References:

1. Gutierrez Y. Cysticercosis, Coenurosis and sparganosis. In "Diagnostic pathology of parasitic infections with clinical correlations" Edited by Gutierrez Y. pp452-458 Lea & Febiger 1990
2. Sparks AK, Neafie RC, Connor DH. Sparganosis. In "Pathology of tropical and extraordinary diseases" vol. 2. Edited by Binford CH & Connor DH. pp534-538. Armed Forces Institute of pathology, Washington, D.C., 1976.
3. Wang LT, Cross JH. Human sparganosis in Taiwan--a report of two cases. J Formosan Med Assoc. 73 : 173-177, 1974
4. Liao SW, Lee TS, Shih TP, Ho WL, Chen ER. Proliferating sparganosis in lumbar spine-- a case report. J Formosan Med Assoc 83 : 603-611, 1984

Comparative Pathology Case 21

Contributor: Ching-Ho Wang (王金和), DVM., MS, PhD

Professor, Department of Veterinary Medicine, National Taiwan University

Clinical History: Case 1. Broiler, 5 weeks old, from a ranch with 50,000 chickens. Two times of (Newcastle disease) ND vaccination had been performed during growing. Severe respiratory signs, greenish diarrhea and death were noted from the age of 4 weeks. More than 800 heads died per day. The disease lasted for 2 weeks till reaching market size (6 weeks old). Half of the chickens died during this outbreak.

Case 2. One of the 57-week-old chickens in a breeder chicken ranch. There were 5,800 chickens in this flock. All chickens were vaccinated with ND vaccine for several times. Nine of them died suddenly. Disease in feed intake, respiratory signs, and drop of egg production were noted in the following days. Sick chickens showed nervous signs of tilt neck and shaking head. Mortality reached 1.5% daily. Finally all of them were discarded (A2265).

Diagnosis: Newcastle disease

Gross Findings: Case 1. Severe tracheal congestion and air sacculitis were noted in most affected chickens. Hemorrhagic lesions were found in the papillae and transitional parts of proventriculus, and in duodenum, jejunum, ileum and cecal tonsils. Several plaques, 0.5 x 1.0 x 0.3 cm, of fibrinous-necrotic exudate covered the mucosa of small intestine.

Case 2. Some chickens showed increase of tracheal secretion and white exudate in air sacs in necropsy. Other organs were grossly normal except one chicken showed hemorrhage in the ovary.

Histopathological Findings: Case 1. Hemorrhagic-necrotic lesions were seen in the small intestine. The severely necrotic tissues were mixed with a lot of fibrin and many inflammatory cells. Severe hemorrhage was found around the necrotic lesions.

Case 2. Mononuclear cells infiltrated around the blood vessels in the meninges at the basal part of the brain stem. Heterophils and other inflammatory cells infiltrated in the hemorrhagic ovary.

Immunochemistry Results: Indirect avidin-biotin complex stain showed positive reactions in the tracheal and enteric epithelial cells.

Discussion: Newcastle disease virus (NDV) belongs to avian paramyxovirus. Although only one serotype is found, there are five pathotypes according to its pathogenicity. The first 2 velogenic types are viscerotropic velogenic NDV (VVNDV) and neurotropic velogenic NDV (NVNDV). The first case belongs to VVNDV and the second case belongs to NVNDV. Both viruses cause severe disease in chickens as well as other birds around the world. The mortality reaches 100% in non-vaccinated chickens. There was a severe outbreak in Taiwan during the late 1994 and early 1995.

Although the primary hosts of ND infection are chickens and other avian species, human cases of Newcastle disease have been reported as early as 1943. Over 37 reports on human infection have been published (Chang, 1981). Human infections usually resulted from laboratory or vaccination accidents, or handling of infected chickens. The symptoms in human patients are usually mild and confined to conjunctivitis. The incubation period of human cases has usually been 1 to 2 days. Symptoms in patients are commonly limited to the transient, usually unilateral, conjunctivitis without the involvement of the cornea. Human infection usually results in production of low levels of neutralizing antibodies but frequently without detectable HI antibodies (Miller, 1971).

Diagnosis Criteria: Hemorrhages in specific sites of the alimentary tract are pathognomonic for VVND. These lesions are often more prominent in the proventriculus, cecum, and small intestine. Hemorrhages appear to be resulted from necrosis. Aside from minimal air sac inflammation, there are always no gross lesions in chickens with NVND; however, the nervous signs are quite diagnostic.

References:

1. Alexander, D.J. 1989. Newcastle disease. In A Laboratory Manual for the Isolation and Identification of Avian Pathogens. 3rd ed., Purchase H.G. (ed.), Kendall Hunt Publ. Co., Dubuque, Iowa, U.S.A., pp. 114-123.
2. Alexander, D.J. 1990. Avian paramyxoviridae-recent developments. Vet. Microbiol. 23: 103-114.
3. Alexander, D.J. 1995. Newcastle disease in countries of the European Union. Avian Pathol. 24: 3-10.
4. Chang P.W. 1981. Newcastle disease. In J.H. Steele (ed) Viral zoonoses, Series in Zoonoses 2. CRC Press, Boca Raton, Fla. pp 261-274.

5. Ojeh, C.K. and H.O. Okoro. 1992. Isolation and characterisation of Newcastle disease virus strain in a feral dove (*Stigmatopelia senegalensis*) in Nigeria. *Trop. Anim. Hlth. Prod.* 24: 211-215.
6. Wang C.H. 1992. Application of immunoperoxidase staining for Newcastle disease virus. *J. Chinese Soc. Vet. Sci.* 18: 87-92.

Comparative Pathology Case 22

Contributors:

PH Chang¹ (張本恒), SH Lee² (李淑慧), MH Jong² (鍾明華),
HC Chiang³ (蔣先冲), CH Cheng¹ (鄭穹翔)

1. Department of Veterinary Medicine, College of Agriculture, National Taiwan University, Taipei, 106, Taiwan.
2. Taiwan Provincial Research Institute for Animal Health, Tansui, Taiwan.
3. I-Lan Livestock Disease Control Center, I-Lan, Taiwan

Clinical History: A brood stock-production hatchery rearing both goldfish and koi carp in earthen and concrete ponds. One pond of 70,000 goldfish fry showed anorexia, gasping, and lethargy. Affected fry became yellowish pigmentation before death. The mortality was approximately 100%.

Diagnosis: Herpesvirus infection of goldfish

Histopathological Findings: The head kidney revealed multiple focal liquefactive necrosis with mild infiltrate of large nucleus cells and inflammatory cells. The large nucleus cells showed prominent chromatin margination. Similar lesions were found in the heart, the lamina propria of small intestine, and the pancreatic islets. In addition to focal necrosis in the parenchyma, the trunk kidney also had focal hyalin droplets deposition in renal tubules epithelia.

Electron Microscopic Findings: Transmissible electron microscope examination of the head kidney revealed herpesvirus-like particles presented in the large nucleus cells around necrotic areas. There were naked particles in the nucleus and enveloped particles in the cytoplasm. The sizes of the naked and enveloped particles were 90 to 120 nm in diameter, respectively. In negative stains of pooled visceral organs, round-shaped virions were observed, the virus was identified as herpesvirus.

Experimental Infection: A cytopathic agent was isolated from pooled visceral organs of experimentally inoculated goldfish. This isolate resembled in morphologic appearance to the virus originally isolated from goldfish.

Discussion : The size and shape of the virions were consistent with previous observations of herpesviruses associated with herpesviral hematopoietic necrosis of

goldfish described by Jung and Miyazaki. They also reported similar epizootiology in goldfish in Japan.

This is the first case of herpesvirus infection of goldfish in Taiwan. More research should be done to study its pathogenesis.

References:

- 1.Sano, T., H. Fukuda, M. Furukawa, H. Hosoya, and Y. Moriya. 1985. A herpesvirus isolated from carp papilloma in Japan. In Fish and shellfish pathology. A. E. Ellis (ed.). Academic Press, London, England, pp. 307-311.
- 2.Hedrick, R. P., and T. Sano. 1989. Herpesviruses of fish In Viruses of lower vertebrates. W. Ahne and E. Kurstak (eds.). Springer-Verlag, Berlin, Federal Republic of Germany, pp. 161- 170.
- 3.Jung, S. J., and T. Miyazaki. 1995. Herpesviral haematopoietic necrosis of goldfish, *Carassius auratus* (L.). J. Fish Dis. 18: 211-220.

Comparative Pathology Case 23

Contributor : HL Chen (陳小玲) , MD

Chief resident, Taipei Institute Of Pathology

Clinical History : A 72-year-old retired farm woman presented with multiple firm papules, measuring 0.2 to 0.9 cm, on an erythematous base over left forearm, which she noted 2 to 3 months prior to seeking medical assistance. There is no history of recent trauma to the affect area.

Diagnosis : Chromomycosis (also known as Chromoblastomycosis) .

Histopathological Findings : The skin shows acanthosis of epidermis and granulomas in the papillary and upper reticular dermis. The granulomas are composed of epithelioid histiocytes and multinucleated giant cells. Some of the granulomas have central collections of neutrophil and give rise to features of suppurative granulomas. Fungal bodies, which are dark brown, thick-walled ovoid bodies with occasional wall septation, are observed. Transepithelial elimination of fungal bodies to the surface and hair follicles are evident.

Histochemical studies :

The chitin wall of fungi characteristically gives positive reaction to periodic acid-Schiff reaction and Gomori's methenamine silver stain.

Discussion : Chromomycosis (Chromoblastomycosis) is a chronic, cutaneous fungal infection, caused by a group of pigmented, saprophytic fungi that may be isolated from soil, wood and rotting vegetation. Initial infection follows traumatic transepithelial inoculation of fungi. The disease is subsequently disseminated via lymphatic and autoinoculation. The lesions develop so slowly that when patients eventually seek medical care, they may not recall the trauma. The majority of cases occur in the tropics and subtropics, but isolated cases have been reported in temperate zones. Five species of dermatiaceous (black) fungi cause chromomycosis, and are typed according to specific morphological characteristics of sporulation, which are evident on culture. *Fonsecaea pedrosoi* is the most prevalent of the five, and *Phialophora verrucosa*, *Cladosporium carrionii*, *Fonsecaea Compacta* and *Rhinochlamydia cerophila* occur in descending order of frequency. The clinical features are characterized by verrucous, crusted or ulcerated lesions. The lesions are usually on the lower leg, but may occur anywhere on the body where

trauma has been inflicted. Chromomycosis typically involved upper dermis and epidermis ; deep dermal and subcutaneous infection is rare and presumably reflects the depth of the initial inoculating dose of fungi. Haematoxylin and eosin stains of sections taken from the lesions show hyperkeratosis, irregular acanthosis and pseudoepitheliomatous hyperplasia. The characteristic tissue reaction is a mixed purulent and granulomatous type associated scattered fungal bodies, which are chestnut brown in color, spherical, thick-walled with occasional septation. Transepithelial elimination of the fungal bodies is specific to chromomycosis, which results in the characteristic clinical features of "black dots" within the epidermis of affected areas. Treatment of chromomycosis is difficult and includes wide excision of affected area, and use of physical agents such as carbon-dioxide laser, cryo and heat therapy. Prolonged treatment with systemic anti-fungal agents alone, and in combination, provides the best chance of cure. Itraconazole is a relatively new systemic antifungal agent, which is highly lipophilic, and thus preferentially redistributes to skin. Inhibition of cytochrome P-450, crucial for ergosterol synthesis, leads to a cascade of abnormalities in membrane permeability, membrane-bound enzyme activity, and co-ordination of chitin synthesis.

Diagnostic Criteria :

1. Direct examination of pus or scale and histopathological examination of affected skin : identification of fungal bodies.
2. Culture : for specific identification and confirmation of the histopathological diagnosis.

References :

1. Smith C.H. J.N., Barker W.N. and Hay R.J. : A case of chromoblastomycosis responding to treatment with itraconazole in : British J. of Dermatol 1993;128 : 436-439.
2. Walter F. Lever. Histopathology of the Skin 7ed. P376-378.
3. Binford C.H. and Lonner, D.H. Pathology of Tropical and Extraordinary Disease 2nd ed. AFIP, P858-586.
4. Ramzi S. Cotran ed. al, Robbins Pathologic Basis of Disease 4th ed. P396.
5. Rosai J et al. Ackerman's Surgical Pathology 7th ed. P61.

Comparative Pathology Case 24

Contributor : SS Yeh (葉祥森), MD

Visiting Staff, Department of Pathology, Provincial Hsinchu Hospital

Clinical History : This patient is an 85-year-old female. She suffered from enlarging bulging mass in left buttock since about 2 years ago. Medical treatment did not alleviate this problem. X-ray and CT scan study showed a huge osteolytic tumor, 17 x 17 x 10 cm, in sacroiliac joint area with destruction of regional muscles. Sonographic examination of the thyroid gland revealed three small nodules, up to 0.7 cm in greatest dimension, suggestive of nodular goiter. There is no neck lymphadenopathy and no other related significant abnormality could be found in chest X ray or other diagnostic workup.

Diagnosis : Metastatic thyroid carcinoma, possibly follicular type

Gross Findings : Not available

Histopathologic Findings: Sheets of tumor cells forming microfollicular structures with colloid content in some of them . Muscle was infiltrated by tumor cells and occasional intravascular permeation was noted. The features are those of a metastatic thyroid carcinoma in follicular type.

Immunohistochemical Results : Monoclonal antibody against thyroglobulin showed strong positive reaction in the follicular epithelial cells and weak reaction in the colloid. This further proves that this is a metastatic thyroid carcinoma, either from a papillary carcinoma or follicular carcinoma.

Discussion : Thyroid cancer is the most common form of endocrine malignancy. It constitutes 1.3 % of all malignancies in USA, yet it accounts for only 0.4 % of cancer deaths. The age range is from children to elderly. The ratio of female to male is about 2.5:1. The major subtypes of classification is papillary carcinoma, which accounts over 50 % of the cases, and follicular carcinoma, which ranges from 5 % to 40 % depending on geographic and dietary factors. Some reports demonstrated the increased rate in goiter prevalent areas. The mean age at the time of diagnosis for papillary carcinoma is 31 to 49 years, while that for follicular subtype is about 10 years older.

Thyroid carcinoma has general unique features:

1. It is a slow-growing tumor which bears relatively good prognosis even when there is extensive regional lymph node metastasis, especially for young age group (up to 60 %).
2. There is high occult carcinoma rate in autopsy studies ranging from 5 % to 28 %. The definition of occult carcinoma is tumors equal to or less than 1.5 cm, regardless of whether or not they are palpable. Most of the occult carcinoma is papillary type.
3. The disease can be latent after primary treatment for 20-30 years when it recurs or deadly spreading follows.
4. In well differentiated follicular carcinoma, it is difficult to distinct from its benign counterpart. Throughout sampling and examination of the capsule to identify capsule invasion and blood vessel permeation is mandatory to diagnose a minimally invasive follicular carcinoma.

Occult thyroid carcinoma with metastasis is rare but well documented. The smallest tumor ever metastasized was less than 1 mm in size. Most of the metastatic location is the regional neck lymph nodes. Distant metastasis, mostly to bone and/or lungs, with lethal outcome is occasionally reported. Both the papillary and follicular subtypes are incriminated. The primary lesion could be diagnosed as goiter or other benign lesions without pathological backup. Most of the presenting problems for patients are neck lymph node enlargement or lung nodules or mass formation in bone causing pain. This kind of cancer of unknown primary tumor site (CUP) is a common clinical syndrome, accounting for approximately 5-10 % of cancer diagnoses. The primary sources are frequently in the lungs, breast and prostate. The initial approach for CUP is thorough physical examination, image analysis and good biopsy specimen for light microscopic examination. With the help of immunostaining for thyroglobulin, the diagnosis of metastatic thyroid carcinoma is no longer a problem. Serum level of thyroglobulin is not useful for diagnosis because of the overlapping between cancer and other benign processes, like follicular adenoma, Hashimoto's disease, etc. However, it still has its value in follow-up. Thyrotoxicosis is exceptional, but was reported mostly in the cases with massive distant metastases. Papillary carcinoma is often multicentric and tends to spread via lymphatic channels to regional lymph nodes. Follicular carcinoma, on the contrary, is usually solitary and uses hematogenous way to reach distant sites; hence, true embolic lymph node metastases are exceedingly rare. This distinction is hard to explain.

The fact that regional lymph node metastasis does not significantly decrease the survival rate (overall, more than 95 %) and that cervical lymph node involvement

and cervical recurrence are frequent before discovery of distant metastases show that lymph node metastasis is an indicator, but not governor of survival. However, distant metastasis is an ominous sign and could be bone, lungs, brain and liver.

The prognostic factors:

1. Extensive distant metastases.
2. Older age at the discovery of the metastases
3. Absence of radioiodine uptake by metastases.
4. Moderately differentiated follicular cell type.

Treatment : Integrated modalities of treatment are necessary, including orthopedic surgery (complete tumor excision), radioiodine therapy, and external irradiation. Late emergence of metastasis was reported, up to 41 years after initial treatment, indicating that close follow-up is needed in the first years, but regular detection is still necessary indefinitely.

Diagnostic Criteria :

1. Tumor follicles with colloid content, reminiscing thyroid tissue.
2. Reaction for anti-thyroglobulin immunostaining.

References :

1. Beaugie JM, Brown CL, Doniach I, Richardson JE. Primary malignant tumors of thyroid: The relationship between histological classification and clinical behavior. *British Journal of Surgery*. 63:173-181, 1976.
2. Brage ME. Simon MA. Evaluation, prognosis, and medical treatment considerations of metastatic bone tumors. [Review] *Orthopedics*. 15(5):589-96, 1992 May.
3. Cady B. Lymph node metastases. Indicators, but not governors of survival. [Review] *Archives of Surgery*. 119(9):1067-72, 1984 Sep.
4. Chen KT. Minute (less than 1 mm) occult papillary thyroid carcinoma with metastasis [letter]. *American Journal of Clinical Pathology*. 91(6):746, 1989 Jun.
5. Daugaard G. Unknown primary tumours. [Review] *Cancer Treatment Reviews*. 20(2):119-47, 1994 Apr.
6. Elgart GW. Patterson JW. Taylor R. Cutaneous metastasis from papillary carcinoma of the thyroid gland [see comments]. [Review] *Journal of the American Academy of Dermatology*. 25(2 Pt 2):404-8, 1991 Aug.
7. Franceschi S. La Vecchia C. Thyroid cancer. [Review] *Cancer Surveys*. 19-20:393-422, 1994.

- 8.Harach HR. Franssila KO. Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer.* 56(3):531-8, 1985 Aug 1.
- 9.Hoie J. Stenwig AE. Kullmann G. Lindegaard M. Distant metastases in papillary thyroid cancer. A review of 91 patients. *Cancer.* 61(1):1-6, 1988 Jan 1.
- 10.Lang W. Borrusch H. Bauer L. Occult carcinomas of the thyroid. Evaluation of 1,020 sequential autopsies. *American Journal of Clinical Pathology.* 90(1):72-6, 1988 Jul.
- 11.Leonard RJ. Nystrom JS. Diagnostic evaluation of patients with carcinoma of unknown primary tumor site. [Review] *Seminars in Oncology.* 20(3):244-50, 1993 Jun.
- 12.Marcocci C. Pacini F. Elisei R. Schipani E. Ceccarelli C. Miccoli P. Arganini M. Pinchera A. Clinical and biologic behavior of bone metastases from differentiated thyroid carcinoma. *Surgery.* 106(6):960-6, 1989 Dec.
- 13.McGregor GI. Luoma A. Jackson SM. Lymph node metastases from well-differentiated thyroid cancer. clinical review. *American Journal of Surgery.* 149(5):610-2, 1985 May.
- 14.Niederle B. Roka R. Schemper M. Fritsch A. Weissel M. Ramach W. Surgical treatment of distant metastases in differentiated thyroid cancer: indication and results. *Surgery.* 100(6):1088-97, 1986 Dec.
- 15.Ruddon RW. Norton SE. Use of biological markers in the diagnosis of cancers of unknown primary tumor. [Review] *Seminars in Oncology.* 20(3):251-60, 1993 Jun.
- 16.Schlumberger M. Tubiana M. De Vathaire F. Hill C. Gardet P. Travagli JP. Fragu P. Lumbroso J. Caillou B. Parmentier C. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *Journal of Clinical Endocrinology & Metabolism.* 63(4):960-7, 1986 Oct.
- 17.Schlag PM. Hunerbein M. Cancer of unknown primary site. [Review] *Annales Chirurgiae et Gynaecologiae.* 83(1):8-12, 1994.
- 18.Schroder S. Pfannschmidt N. Bocker W. Muller HW. de Heer K. Histopathologic types and clinical behaviour of occult papillary carcinoma of the thyroid. *Pathology, Research & Practice.* 179(1):81-7, 1984 Sep.
- 19.Steckel RJ. Kagan AR. Metastatic tumors of unknown origin. [Review] *Cancer.* 67(4 Suppl):1242-4, 1991 Feb 15.
- 20.Strate SM. Lee EL. Childers JH. Occult papillary carcinoma of the thyroid with distant metastases. *Cancer.* 54(6):1093-100, 1984 Sep 15.

21. Yamamoto Y. Maeda T. Izumi K. Otsuka H. Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases. *Cancer*. 65(5):1173-9, 1990 Mar 1.
22. Zohar Y. Strauss M. Occult distant metastases of well-differentiated thyroid carcinoma. *Head & Neck*. 16(5):438-42, 1994 Sep-Oct.

Comparative Pathology Case 25

Contributor : CC Lee (李進成), MD, PhD

Visiting Staff, Department of Pathology, Hsin-Kwang Hospital

Clinical History: A 70 years old male patient has been suffered from acute onset numbness over right nasal area, cheek, gum and hard palate when he was eating for 2 months. Brain MRI showed a heterogeneous mass occupying sphenoid and right posterior ethmoid sinus. The biopsy was done trans-sphenoidally by surgeons.

Diagnosis: Chordoma, skull base

Histopathological Findings: The specimen submitted consists of multiple fragments of whitish and soft tissue with myxoid material measuring 0.3 x 0.3 x 0.2 cm. in size. Section shows lobules of sheets or cords of variably sized vacuolated polygonal (physaliferous) cells with distinct cell borders and single or multiple large clear cytoplasmic vacuoles in a mucoid matrix. The lobules are separated by thin fibrous septa. Nuclei were round to oval with stippled to clumped chromatin. Several destroyed trabecular bone and sinus mucosa are also noted. Histochemical study shows that the tumor cells contain periodic- acid-Schiff positive granules in their cytoplasm and the extracellular mucin stained blue with Alcian blue stain.

Immunohistochemical Results: Immunohistochemical staining shows that the tumor cells are reactive against cytokeratin, epithelial membrane antigen, S-100 and vimentin antibodies.

Discussion: Chordomas arise along an archipelago of notochordal remnants extending from the region of the sella turcica to their caudal extreme in the sacrum. The tumor are unevenly distributed along the craniospinal axis; approximately half arise in the sacrum, one third in the spheno-occipital region or clivus, and the remainder in the articulating vertebrae. Intracranial lesions, midline and often destructive of clivus, generally produce headache and cranial palsies, particularly diplopia. Cranial nerve signs are often unilateral. Sacral chordomas are destructive intrasacral tumors which produce pain, sphincter disturbance, and neurological symptoms from pressure upon regional nerve roots.

References:

1. Peter C. Burger and Bernd W. Scheithauer Tumors of the Central Nervous System AFIP, 1994. pp. 303-306
2. Miettinen M, Lehto VP, Dahl D, Virtanen I. Differential diagnosis of chordoma, chondroid, and ependymal tumors as aided by anti-interfilament antibodies. Am J Pathol 1983; 112:160- 9.
3. Forsyth PA, Cascino TL, Shaw EG, et al. Intracranial chordomas: a clinicopathologic and prognostic study of 51 cases. J neurosurgery 1993; 78:741-7

Comparative Pathology Case 26

Contributor : CC Lin (林正忠) , DVM, MS

Department of Veterinary Medicine, National Chung Hsing University

Clinical History : A farm raised about 3,000 pigs in the center of Taiwan. The weaned pigs (about 50-60 days old) showed signs of high fever, yellowish diarrhea, dyspnea and nervous sign for about one week. The morbidity of the weaned pigs was 25% ; and mortality was 60%. The pigs had been treated with amoxicillin, nalidixic acid, OTC and chloramphenicol ; but without obvious improvement. The owner sent two dead pigs to NCHU Veterinary Teaching Hospital for pathological diagnosis.

Diagnosis : Swine Salmonellosis (septicemic form)

Gross Findings : Both of the carcasses showed discoloration of the skin and ears. Lungs were firmer, darker and uncollapsed. Lots of pinpoint size white spots scattered on the livers. The mucosa of the terminal ileum to colon were partially covered by yellowish membrane and lumen contained watery brownish feces with septic tank odour. Mesenteric lymph nodes were swollen 2-3 times of normal size.

Histopathological Findings : The livers revealed multifocal cytolytic necrosis, with a few neutrophils infiltration. There were numerous mononuclear cells infiltrated in the sinusoid of livers (paratyphoid nodules). The lungs revealed mild bronchiolitis but alveolar septa were widened by edematous fluid and some mononuclear cells. The superficial mucosal epithelium of the intestine was necrotic and sloughed, which was mixed with fibrin. The microabscesses could be found in the cerebrum.

Discussion : In swine salmonellosis is caused by the genus *Salmonella*. They are classified into named serotypes by antigenic factors present on their O or somatic antigens on their H or flagellar antigens. Final differentiation within species is carried out by phage typing.

Salmonellosis assumes one of the following forms : peracute septicemia, acute enteritis, chronic enteritis, or subclinical carrier state. Some important syndromes caused by *Salmonella* serovars are listed below :

Group A *S. paratyphi* A Paratyphoid fever in humans

Group B	S.schottmuelleri	Paratyphoid fever in humans
	S.typhimurium	Gastroenteritis in humans ; most prevalent species causing infections in various animal species
	S.abortus-equi	Abortion in mares and jennets
	S.abortus-bovis	Abortion in cattle
	S.abortio-ovis	Abortion in sheep
Group C1	S.choleraesius	Enteritis in pigs ; frequent secondary invader in hog cholera ; infections in humans
	S.typhisuis	Intections in young pigs.
Group C2	S.newport	Infections in humans various animals, and especially cattle
Group D1	S.entcritidis	Infectiorts in various animals ; gastroenteritis in humans
	S.gallinarum	Fowl typhoid, an acute intestinal disease of young chickens and turkeys.
	S.Pullorum (pullorum)	Severe intestinal infcctions of chicks and poults ; chronic infections in older fowl
	S.typhi	Typhoid fever in humans
	S.dublin	Severe infections in calves
Group E1	S.anatum	Keel disease in ducklings

Diagnosis Criteria :

1. Multifocal paratyphoid nodules ; which are characterized by cytolytic nccrosis and monocyte (RE cell) infiltration.
2. Button ulcer always in company with hog cholera.
3. Bacteria isolation from bile duct.
4. Salmonellae serotyping.

References :

1. Cartcr G.R, John R. Cole, Jr. Enterobacteria, Diagnostic Procedures in Veterinary Bacteriology and Mycology 5th ed., Academic Press, California, U.S.A., 111-113, 1990.
2. Taylor D.J., Salmonellosis, Pig diseasc 5th ed., Burlington Press, Foxton, Cambridge, UK, 100-104, 1989.

Comparative Pathology Case 27

Contributor : YT Chiu (邱雲棕), DVM, MS

Department of Pathology, Pig Research Institute, Taiwan

Clinical History : The submitted tissue was from one of collected 23 pigs which came from a breeding farm and nuclear breeding center of North Taiwan on routine necropsy. Those pigs were from 6 weeks to 2 years of age. The breed included 12 hybrid, 5 Landrace, 4 Yorkshire and 2 Duroc. 13 pigs were male and 10 pigs were female. Some of the affected pigs showed depression, poor-growth, dyspnea, and cyanosis, but in others no symptom could be found before sudden death. There were 8 pigs revealing joint enlargement and lameness. The sick pigs had been treated by antibiotics, but with poor efficacy.

Diagnosis : Vegetative valvular endocarditis associated with valvular malformation.

Gross Lesions : In external appearance, the heart revealed remarkable hypertrophy or dilation of left or right ventricle and atrium. The opened affected hearts there were friable, cauliflower-like, pink or red vegetation which loosely or firmly attached to the mitral (15 pigs), aortic (11 pigs), tricuspid (7 pigs) or pulmonary (2 pigs) leaflets. We also found leaflets with or without adhesion of the vegetation, those leaflets revealing long, thin or short, stout chordae tendinae, upwardly aligned papillary muscles. Malformed moderate band was thick short and connected the septum and right ventricular free wall. Multiple infarction was occasionally found in the papillary or trabeculae muscle.

Most affected pigs with endocarditis also usually showed systemic bacterial infection. Those lesions included epicarditis, pleuritis, polyarthritis, polyserositis, pneumonia and renal infarction.

Histopathological Findings : The vegetation was mainly composed of amorphous strands of fibrin, cellular debris, neutrophils, lymphocytes, macrophages, platelets, and bacterial clumps which usually occurred as islands surrounded by fibrin or as a mat lining the surface of the vegetation. Those inflammatory cells formed a dense zone between the valve stroma and the admixture of bacteria with fibrin which formed the greater part of the vegetation. The valvular stroma or spongiosa showed remarkable edema, necrosis and proliferation of angioblast with fibroblast, there are some fibrinous microthrombi were noticed in small vessels of the leaflets. Vasculitis with thrombosis was markedly found near the infarction area which frequently

occurred in the left ventricle, septum or apex. Sometimes, the disorientation of myocytes, thickness of intramural coronary artery, myocardial necrosis, or fibrosis and myocarditis were also noticed in both ventricles and septum. The lesions of valvular malformation were characterized by proliferation of the spongiosa, hypoelastification, irregular arrangement of fibrosa and edema of stroma. The silver impregnated staining examination for cardiac matrix in both ventricle and septum myocardium. According to different gross lesions. The remodeling of cardiac matrix could be divided into three kinds: 1) In hypertrophic heart, there were marked increases of all component (strut, coil, weave) of cardiac matrix, characterized by thickness, density, and irregular arrangement or disorganization, 2) In dilated heart, all component of matrix was thinned, disrupted, and decreased in number, and 3) Fewer or disappeared components of matrix were present in the area of myocardial infarction and myocarditis.

Bacterial isolation :

No of pigs	Bacterial isolation of vegetation	Bacterial isolation of other complications
4	<u>Streptococcus suis</u>	epicarditis (n=4), polyserositis (n=2), arthritis (n=2)
7	β -haemolytic <u>streptococcus</u>	epicarditis (n=5), polyserositis (n=1), arthritis (n=4), pleuritis (n=3)
4	<u>E. rhusiopathiae</u>	glomerulonephritis (n=2), spleen enlargement (n=3)
2 (n=1)	<u>Staphylococcus epidermidis</u>	epicarditis (n=1), no done
2	<u>E. coli</u>	no done
1	<u>Salmonella choleraesuis</u>	hepatic necrosis

Discussion : Bacterial endocarditis has been found in human, pig, cat, dog, and cow. There are two factors necessary for causing bacterial endocarditis: an occurrence of bacteraemia or septicemia must coincide with small thrombi on the valve. Because of valvular abnormality can induce valvular regurgitation, and then produce haemodynamic changing and turbulent blood flow. Those condition at particular risk all involve high pressure flow likely to lead to endocardial or

valvular damage which is initially established by endocarditis. In human, several laboratories have proved the risk of endocarditis in patient of mitral regurgitation. In human, when a patient suffers mitral valve prolapse, easily infected with valvular endocarditis. Therefore we think that will be a good animal model to study the pathogenesis of bacterial endocarditis associated with valvular malformation.

Diagnostic Criteria :

1. Vegetative endocarditis
2. Valvular malformation
3. Bacterial isolation
4. Systemic infection

References :

1. Bonagura JD, and Pipers FS. Echocardiographic features of aortic valve endocarditis in a dog, a cow, and a horse. J. Am. Vet. Med. Associ. 182:595-599, 1983.
2. Buergeit CD, Cooley AJ, Hines SA, Pipers FS. Endocarditis in six horses. Vet. Pathol. 22:333-337, 1985.
3. Calvert CA. Valvular bacterial endocarditis in the dog. J. Am. Vet. Med. Associ. 180:1080-1084, 1982.
4. Deway HA, Jones MR, Griffin SG, Oxley A. A study of experimental endocarditis in pig. J. Comp. Pathol. 97:567-574, 1987.
5. Durack DT. Experimental bacterial endocarditis. J. Pathol. 115:81-89, 1975.
6. Frary CJ, Devereux RB, Kramer-Fox R, Roberts RB, and Ruchlin HS. Clinical and health care cost consequences of infective endocarditis in mitral valve prolapse. J. Am. Cardiol. 73:263-267, 1994.
7. Factor SM, and Robinson TF. (1988) Comparative connective tissue structure-function relationships in biologic pumps. Lab. Invest. 58:150-156.
8. Factor SM, Butang J, Sole M, Wigle D, Williams WC, and Rojkind M. Pathologic fibrosis and matrix connective tissue in the subaortic myocardium of patients with hypertrophic cardiomyopathy. J. Am. Coll. Cardiol. 17:1343-1351. (1991).
9. McGee James O'D, Isaacson PG and Wright NA. Oxford textbook of pathology. Vol.2a P869-878. (1992).
10. Johnson CM, Bahn RC, and Fass DN. Experimental porcine infective endocarditis: Description of a clinical model. Vet. Pathol. 23:780-782, 1986.
11. Jones J.E.T. Bacterial endocarditis in the pig with special reference to streptococcal endocarditis. J. Comp. Pathol. 90:11-27, 1980.

- 12.Jones J. E. T. Experimental streptococcal endocarditis in the pig. The development of lesions 3 to 14 days after inoculation. J. Comp. Pathol. 91:51-62, 1981.
- 13.Liu SK and Tilley LP. Malformation of canine mitral valve complex.(1975) J. Am. Vet. Med. Associ. vol.167 No.6 465-471.
- 14.Liu SK and Tilley LP. Dysplasia of tricuspid valve in dog and cat.(1976) J. Am. Vet. Med. Associ. vol.169 NO.6 623-629.
- 15.Liu SK, Chiu YT, Fox PR Factor SM, Shyu JJ, and Chu RM.(1994) Interstitial connective tissue abnormalities in feline. Cardiomyopathies. Lab. Invest. 70:20.
- 16.Roth L. Bacterial aortic valvular endocarditis associated with subaortic stenosis. J. Small Ani. Prac. 35:169-172, 1994.
- 17.Schueler RL, Morehouse LG, Plson LD. Intravenous exposure of swine to group E streptococci: Articular and cardiac lesions associated with experimentally induced septicemic infection of swine with group E streptococci. Am. J. Vet. Res. 33:1801-1812, 1972.
- 18.Sisson D, and Thomas WP. Endocarditis of the aortic valve in the dog. J. Am. Vet. Med. Associ. 184:570-577, 1984.
- 19.Weber KT, Sun Y, Tyagi SC and Cleutjens PM. Collagen network of the myocardium: Function, structural remodeling and regulatory mechanisms. J. Mol. Cell. Cardiol. 26:279-292, 1994.