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Learning objectives

1. To understand a developmental mechanism of the drug-related visceral disorders (DVDs) in the abdomen.
2. To review pictorial examples of common and uncommon conditions of DVDs.
Background

Recently, various new therapies using newly developed drugs mainly the molecular target drug and anticancer drug are introduced into the daily clinical practice. In tandem with the penetration of these new therapies, the new drug-related visceral disorders (DVDs) have been reported as the side effects of them.

In DVDs, specific image findings are sometimes shown: radiological images are useful not only in early detection of DVDs, but also for decision and follow-up of the treatment strategy for DVDs.

There are wide ranges of DVDs in the abdomen according to the processes of metabolism and/or the administration routes of drugs as follows:

1. Disorders due to antibiotics (biliary pseudolithiasis, pseudomembranous enteritis).
2. Blue or fatty liver due to local/systemic chemotherapy of the anticancer drugs.
3. Amiodarone liver due to the antiarrhythmic drug.
4. Compression fractures of thoracolumbar spine due to chronic administration of steroid.
5. Internal anomalies in thalidomide embryopathy such as gallbladder defect and hepatic deformity.
6. Tamoxifen-induced uterine endometrial abnormalities such as polyp, hyperplasia, and cancer.
7. Hemosiderosis or hemochromatosis due to chronic internal use of chalybeate or repeated blood transfusion.
8. Neoplasms such as malignant lymphoma and lymphoproliferative diseases due to the immunosuppressive drugs.

Most of these can be usually detected by unenhanced or enhanced CT or MR imaging; moreover, in cases of neoplasms, disease staging can be easily and correctly performed by additional PET/CT.

In this exhibit, we will classify the DVDs by the developmental mechanism and give an outline from the viewpoint of imaging.
Findings and procedure details

Classification by the developmental mechanism

The DVDs can be classified into direct and indirect ones from the viewpoints of developmental mechanism.

Direct DVDs are associated with increase in local concentration of drugs because of the abnormality of the administration routes or specific drug dynamics including the excretion routes. Most of the associated drugs are cytotoxic drugs (Table 1).

Table 1. Direct mechanisms in DVDs

1. Disorders caused by the hepatic arterial infusion chemotherapy using anticancer drugs (Cytotoxicity)
2. Liver damage (fatty liver or blue liver) caused by the systemic chemotherapy using the anticancer drug (Cytotoxicity)
3. Liver damage caused by the antiarrhythmic drug, amiodarone hydrochloride (Cytotoxicity)
4. Hemosiderosis/hemochromatosis caused by the chalybeate or transfusion (Occurrence of active oxygen molecular species with the iron accumulation within the organ and hyperoxidation of the membrane lipid of the organelle)
5. NSAIDs ulcer (Enzyme inhibition)

Indirect DVDs are associated various drugs as follows: antibiotics, immunosuppressive drug, steroid, and so on. The mechanism of pathogenesis is relatively complicated (Table 2).

Table 2. Indirect mechanisms in DVDs

1. Pseudomembranous enteritis caused by antibiotics (Microbial substitution)
2. Biliary pseudolithiasis caused by ceftriaxone (Rise in concentrations of biliary ionized calcium by the bile acid excretion inhibition)
3. Malignant lymphoma and lymphoproliferative disease associated with immunosuppressive drugs (Induction of the clonal growth of B-cells due to the viral infection or reactivation of inapparent infection virus)

4. Tamoxifen-associated uterine endometrial abnormality (Increased risk of the uterine cancer due to the estrogen effects)

5. Spinal compression fracture caused by chronic administration of steroid (Bone fragility due to the decrease in bone quantity)

6. Internal anomalies of thalidomide embryopathy including gallbladder defect and deformity of liver shape (Teratogenicity by producing oxidative stress/damage, DNA intercalation, inhibition of angiogenesis, and cereblon binding by exposing thalidomide for fetus)

1. Disorders caused by the hepatic arterial infusion chemotherapy using anticancer drugs

Concepts

Transcatheter arterial chemoembolization (TACE) is a therapy, which is widely used for a hepatocellular carcinoma and a hypervascular hepatic metastasis. For hepatocellular carcinoma, embolization using the gelatine sponge following an intraarterial administration of the suspension mixed with iodized oil and anticancer drug (e.g., epirubicin) is widely performed. In recent years, emulsion of Lipiodol and cisplatin are often used for intraarterial infusion. In advanced cases having difficulty in local treatment, continuous arterial infusion chemotherapy by using reservoir system or one-shot infusion treatment of the anticancer drug is performed. For hepatocellular carcinoma, drugs such epirubicin, adriamycin, 5-FU, and cisplatin are used. In contrast, for metastatic liver cancer, drugs such as mitomycin, 5-FU, epirubicin, adriamycin, and cisplatin are used.

Mechanism of pathogenesis and Clinical observation

Complications of TACE include acute hepatitis, liver abscess, biloma (Fig. 1 on page 18), hepatic infarction, cholecystitis, gallbladder infarction, splenic infarction, gastrointestinal mucosal injury, pulmonary infarction, Lipiodol pneumonitis and pleural effusions. The relatively frequent complications are biloma (0.87%), but it is reported that in many cases (75%) size does not have a change or resolved spontaneously. Cholecystitis, gallbladder infarction, hepatic failure, multiple hepatic aneurysms, liver abscess and gastrointestinal mucosal injury is the second frequent. The cholecystitis and gallbladder infarction, hepatic failure, liver abscess, gastrointestinal mucosal injury are responsible for nontargeted injection for cholecystic artery, treatment for poor
liver function cases, extensive embolization for the liver, and inappropriate intraarterial injection for gastrointestinal artery, respectively. In addition, arteriovenous shunt or pleural enhancement on angiography before TACE becomes the important risk factor of the pulmonary complication, especially in TACE via the inferior phrenic artery [1]. As a rare complication, skin panniculitis of anterior abdominal wall, which is caused by the unintended inflow of anticancer drugs into the hepatic falciform ligament artery, is reported (Fig. 2 on page 18). The surgical ligation and/or selective coil embolization of the hepatic falciform ligament artery a reported for prevention [2].

Imaging

In most cases of complications such as liver abscess, biloma, hepatic infarction, cholecystitis, gallbladder infarction, pulmonary infarction, Lipiodol pneumonitis and pleural effusions, abnormal findings are usually seen on the initial abdomen CT: we can predict the occurrence of complications by the fact that highly-concentrated accumulation of Lipiodol is found in the corresponding areas on CT just after TACE.

2. Liver damage (fatty liver or blue liver) caused by the systemic chemotherapy using the anticancer drug

Concepts

In recent years, FOLFOX (folinic acid, fluorouracil oxaliplatin) or FOLFILI (folinic acid, fluorouracil irinotecan) are often used as chemotherapy of colorectal cancer, contributing to prognostic prolongation of colorectal cancer. 5-FU (fluorouracil) is a key drug of 1st line preoperative chemotherapy. The 5-FU administration cause fatty liver at a high probability after 5-FU administration: it is reported that 47% of patients who gave 6-12 cycles showed fatty liver [3]. Also, fatty liver can be caused by all recent chemotherapeutic agents used for colorectal cancer treatment, and it is said that the frequency is the same as 5-FU.

Mechanism of pathogenesis

The main liver damage of oxaliplatin is a sinusoidal obstruction syndrome (SOS) which appears by direct injury of sinusoidal endothelial cells, unlike 5-FU and irinotecan. When the sinusoidal dilatation occurs in 10-78% of cases; many reporters described that the liver macroscopically shows blue because red blood cells are enclosed in the dilated sinusoids of the liver; the condition is called "blue liver". Also, it is known that oxaliplatin results in various disorders of liver parenchyma: nodular reactive hyperplasia and peliotic change are reported. There are reports saying that there is an increase in intraoperative bleeding and transfusion and postoperative complications in patients with SOS; however, many authors described that a prognosis is not influenced by that.
**Clinical observation**

Abnormality of the AST and the ALT may result from the biochemical test, but liver function tests can become normal in lipid hepatitis and SOS.

**Imaging**

Fatty liver is detected by US with 60-94% of sensitivity and 66-95% of specificity. It is also detected by unenhanced CT with 82% of sensitivity and 100% of specificity. However, in lipid hepatitis and SOS, what is the most useful examination among the radiological modalities is not defined [4]. In SOS, an uptake decrease to liver parenchyma in the post-contrast image in SPIO-MRI and an uptake decrease to the liver parenchyma in the hepatobiliary phase in the EOB-MRI are reported. [5, 6]. (Fig. 3 on page 19).

**3. Liver damage caused by the antiarrhythmic drug, amiodarone hydrochloride**

**Concepts**

Amiodarone (AMD) is an antiarrhythmic agent that is effective for refractory ventricular tachyarrhythmia. Both AMD and its metabolite, desethylamiodarone (d-AMD), are accumulated more in the liver than in the spleen and skeletal muscle during AMD therapy. AMD contains iodine and remains long in the liver by inhibiting the phospholipase activity of lysosome in the liver, resulting in increase of CT attenuation of the liver (CTL). Because AMD contains approximately 37.4% of iodine and are fat-soluble, it accumulates to lung, pancreas, liver, heart, and kidneys in addition to the systemic adipose tissues.

**Mechanism of pathogenesis**

It has been pointed out that both AMD and d-AMD may have cytotoxicity responsible for pulmonary fibrosis and hepatic injury [7]. The stagnation time within the liver extends AMD remarkably by inhibiting phospholipase activity of lysosome in the liver tissue; as a result, the level of CT attenuation of the liver increases (Fig. 4 on page 20).

**Clinical observation**

Interstitial pneumonia is a famous serious complication of amiodarone, but attention is also necessary for liver dysfunction.

**Imaging**
It is reported that the X-ray absorption level of the liver correlates with blood drug concentration, and have the role as the biological markers of the blood level. [8]. Relationship between CTL and total dose or dosing period of AMD is controversial.

**Treatment**

Withdrawal of the causing agent, AMD.

**4. Hemosiderosis/hemochromatosis caused by the chalybeate or transfusion**

**Concepts**

Hyperferremia is the disease that iron accumulates in a body from the failure of the iron metabolism regulatory mechanism. It is classified in hereditary hyperferremia and secondary hyperferremia by causative conditions. Secondary hyperferremia is classified into diseases that result in ineffective erythropoiesis (thalassemia, sideroblastic anemia), diseases with the hepatic disorder, diseases due to a large quantity or long-term of transfusion and chalybeate administration, alimentary hyperferremia, and porphyrias. It is also classified into a pattern of accumulation of iron within the reticuloendothelial system such as Kupffer cells of the liver, spleen and bone marrow (previously called hemosiderosis) and a pattern of accumulation of iron within the parenchymatous cells (hemochromatosis).

**Mechanism of pathogenesis**

When intracellular iron excess occurs, free iron which does not bind to protein increases, and this metallic iron promotes the formation of the reactive high active oxygen molecular species such as hydroxyl radical, alkoxy radical and peroxyl radical. It is considered that these active oxygen molecules bring hyperoxidation of the membrane lipid of the organelle, and whose function is injured. It is reported that basically there is no tissue injury in the pattern that iron is accumulated in a reticuloendothelial system and is often caused by iron excess with the transfusion. In contrast, hereditary hyperferremia and ineffective erythropoiesis are main causes in the pattern accumulated to the parenchymatous cells. In the pattern that iron is accumulated in a reticuloendothelial system, iron is accumulated to the spleen and the bone marrow but is not accumulated to the pancreas. In the pattern that iron is accumulated in a reticuloendothelial system, iron is adversely accumulated to the pancreas and the by the pattern accumulated to the parenchymatous cells adversely, but is not accumulated to the spleen and the bone marrow.

**Clinical observation**
Clinically, cirrhosis, diabetes, chromatosis, heart failure are called to be the four chief symptoms. In addition, endocrinopathy (dysfunction of thyroid gland, parathyroid gland and pituitary gland, hypogonadism, amenorrhea and testicular atrophy) and arthropathy (symmetrical swelling and pain of joints) are frequently found.

Imaging

The liver parenchyma diffusely shows high attenuation on unenhanced CT: a high X-ray attenuation value of iron is reflected. On MRI, the organ complicated with ferrugination presents characteristic findings: on T2-weighted image, a low signal is presented; the signal decreases in in-phase of the gradient echo sequence image; and the signal increases in out-of-phase (the opposite direction in fatty liver) [9] (Fig. 5 on page 21). MRI has the highest sensitivity and specificity in diagnosis of iron overload and determination of severity and treatment effects.

Treatment

Bloodletting, iron diet therapy and deferoxamine therapy are performed.

5. NSAIDs ulcer

Concepts

NSAIDs (nonsteroidal anti-inflammatory drugs), adrenocortical hormone, anticancer drug, antimicrobial agent, anti-viral drug, cholinergic agent, and antihypertensive agent are reported as the drug which can exacerbate peptic ulcer. Above all, an NSAID ulcer is most common: NSAIDs is widely used as an analgesic and an antiplatelet agent. It is expected that NSAIDs ulcer will also increase in future because the opportunity using NSAIDs is remarkably increasing for the purpose of the prevention of thrombosis and the treatment for the bone and joint disease.

Mechanism of pathogenesis

It is reported that NSAIDs having effects to inhibit an enzyme called the COX (cyclooxygenase) which inhibits the COX-1, causing the underproductivity of the gastric mucosa defense factor, the prostaglandin (PGE2). In contrary, NSAIDs that selectively inhibit only COX-2 rarely cause a peptic ulcer.

Clinical observation

The NSAIDs ulcer occurs in the early phase of administration with a high rate, especially in the initial first week. It is reported that a gastric ulcer was detected by gastroscopy in 15.5% of the patients with rheumatoid arthritis with NSAIDs administration for more than
three months. The clinical symptoms include epigastralgia, nausea, hematemesis and tarry stools. The frequency of asymptomatic patients is more frequent in NSAIDs ulcer rather than in a non-NSAIDs ulcer due to the helicobacter pylori. The frequency of the NSAIDs ulcer is reported to count 4-43% in patients who do not use preventive medicine together.

**Imaging**

Endoscopy is primarily performed for imaging studies, and there are few cases located in the gastric angle unlike a non-NSAID ulcer. An ulcer often appears in the antrum in cases with long-term administration whereas an ulcer appears in the body in cases with short term NSAID administration. About half of the cases are multiple, and many of them show irregular shape. When NSAIDs are continued, an extremely refractory ulcer may occur. On CT, it is hard to depict many gastric ulcers as far as there are not penetration and perforation, but, with inflammatory change of various degrees of neighboring walls, may present with a cyst of structure of a mucosa defect image and the lumen.

**Treatment**

Withdrawal of NSAIDs and the medical treatment for peptic ulcer; the ulcer is healed relatively easily. When NSAIDs cannot be discontinued, treatments mainly using a proton pump inhibitor and the prostaglandin are provided. Endoscopic hemostasis is performed in the bleeding case, and the transcatheter arterial embolization or surgery are performed in case of failure of hemostasis (Fig. 6 on page 22). Surgery is often performed for the perforation case.

6. **Pseudomembranous enteritis with antibiotics**

**Concepts**

Pseudomembranous enteritis is the most frequent nosocomial infectious disease. The Clostridium difficile infection is classified in to five types: 1) asymptomatic carrier; 2) pure antimicrobial agent-related diarrhea; 3) chronic diarrhea without pseudomembrane; 4) pseudomembranous colitis; and 5) fulminant pseudomembranous colitis [10]. As for the contribution rates of Clostridium difficile in pseudomembranous colitis, antimicrobial agent-related colitis and the antimicrobial agent-related diarrhea, it is estimated with 100%, 60-75%, 10-30%, respectively. Clostridium difficile is anaerobic bacteria and has spores; Clostridium difficile infection results from oral infection upon contact with a spore. The spore exists widely on a bed or the floor of the hospital, and it is detected in 20-70% of the places.
Mechanism of pathogenesis

Microbial substitution caused by antimicrobial agent administration; Clostridium difficile increases, and the toxin produced by this bacteria injures the intestinal mucosa. Tetracyclines, macrolides and new quinolone have a moderate risk in developing Clostridium difficile infection; on the other hand, aminoglycoside, metronidazole and vancomycin has a low risk.

Clinical observation

The main symptom of the pseudomembranous colitis is diarrhea with various degrees ranging from mild to severe. Some patient is complicated with the viscous liquid. The complications are cellulitis, sepsis, abscess, arthritis, dehydration, hypoalbuminemia, and electrolyte abnormality. In the serious cases, toxic megacolon is complicated, causing the fatal clinical condition (the mortality rate, 30-80%).

Imaging

Definitive diagnosis of pseudomembranous enteritis is possible by observing pseudomembrane using endoscopy. 90% of cases of this disease can be diagnosed by endoscopy. The initial endoscopic image is aphthoid colitis, and the accomplished typical image is a white small round membrane (pseudomembrane). The pseudomembrane is generated by the necrotic materials, which can be removed with forceps easily. The common site is rectum and sigmoid colon. In contrast the diagnosis of the Clostridium difficile infection of the non-pseudomembrane type is not easy: it is necessary to differentiate ischemic colitis, other infectious colitis, antimicrobial agent intolerance, antimicrobial agent induced hemorrhagic enterocolitis and inflammatory bowel disease. On CT, abnormal findings may be hard to detect in mild cases; however, in severe cases, significant thickening, edema, mucosal irregularity by the polypoid prominence, peribowel fat stranding, and ascitic fluid are illustrated by CT. It is useful in a determination of the treatment effect. Also, serious complications such as toxic megacolon and GI perforation can be easily diagnosed (Fig. 7 on page 23).

Treatment

In mild cases, the administration of cause antimicrobial agent is discontinued, or we only change it to which antimicrobial agent that aminoglycoside derivative macrolides, nu told to be hard to cause pseudomembranous colitis are quinolone, and a symptom improves 20-25% of patients spontaneously. In moderate cases, metronidazole or vancomycin is administrated when the symptoms are not improved in spite of the withdrawal of the antimicrobial agent. In serious cases, oral administration of high-dose vancomycin is used. If conservative treatment is not valid, or toxic megacolon or GI perforation is detected, the full extraction of large bowel including ileocecal region is performed.
7. Biliary pseudolithiasis caused by ceftriaxone

Concepts

The ceftriaxone (CTRX) is the third generation cefem antimicrobial agent, and has antimicrobial activity resisting gram-negative bacteria and gram-positive bacteria. After administration, 50-60% is excreted in urine, and remaining 20-40% is excreted by bile. It is reported that biliary excretion increases in the patients with renal failure. It has an advantage in that for even patients with renal failure, it can be used without reducing a dose if liver function is normal. Clinical condition after administration of the CTRX includes biliary sludge and gallstones.

Mechanism of pathogenesis

The level of CTRX in the gallbladder after the administration is reported to be 20-150 times high as compared with serum concentration of CTRX, causing bile acid excretion inhibition and increase in biliary ionized calcium concentration. Therefore, a complex of ceftriaxone and calcium is formed, and becomes biliary sludge or gallstones. The incidence is 15-46%. It occurs on day 3-22 after administration and disappears after the administration end spontaneously in 2-63 days. For risk factors of biliary pseudolithiasis, high-dosage (more than 2g/day) or chronic administration, hypercalcemia, fast, total parenteral nutrition, surgical operation and dehydration are cited [11].

Clinical observation

Usually asymptomatic.

Imaging

The image findings of biliary pseudolithiasis are nonspecific. it is accidentally detected by abdominal CT and US ultrasonography. On CT, hyperdense stones are illustrated because of calcium calculus (Fig. 8 on page 24). On US, hyperechoic structures are illustrated, which are accompanied by strong acoustic shadow. Because these image findings are similar to common gallstones, the discrimination only by imaging is difficult. The comparison with the previous images and check-up of the medication history may help diagnose this condition: when gallstones appear in a short term, biliary pseudolithiasis is suspected. As for the complications related to biliary pseudolithiasis, pancreatitis, acute cholecystitis, acute cholangitis and the rise in serum bilirubin level are reported.
Treatment

Not necessary. Only a stopping dosage of CTRX and the follow-up of is enough. In biliary pseudolithiasis, patients have gallbladder sludge, which is excreted little by little spontaneously by gallbladder.

8. Malignant lymphoma and lymphoproliferative disease associated with immunosuppressive drugs

Concepts

Methotrexate (MTX) is placed as an anchor drag of the rheumatoid arthritis (RA) treatment, and it is the most-used antirheumatic drug among DMARDs. MTX has less frequency to develop a side effect than other DMARDs. However, it has serious side effects to have an influence on the vital prognosis including interstitial pneumonia or myelosuppression. In recent years, as a side effect of MTX, occurrence of neoplastic disease called methotrexate-associated lymphoproliferative disorder; MTX-LPD becomes the problem. It is known that in RA patients with malignant lymphoma often complicates at frequency of 2-4 times as compared with general population [12]. In addition, it was found that lymphoproliferative disease including malignant lymphoma was complicated with the patients given MTX, which came to be called MTX-LPD [13]. MTX-LPD is classified as "Other iatrogenic immunodeficiency-associated lymphoproliferative disorders" in immunodeficiency disorder-related lymphoproliferative disease in WHO classification (Table 3) [13].

Table 3. List of immunodeficiency-associated lymphoproliferative disorders

1. Ataxia telangiectasia
   a) Wiskott-Aldrich syndrome
   b) Common variable immunodeficiency
   c) Severe combined immunodeficiency
   d) X-linked lymphoproliferative disorders
   e) Nijimegen breakage syndrome
   f) Hyper-IgM syndrome
2. Autoimmune lymphoproliferative syndrome
3. Lymphomas associated with infection by the human immunodeficiency virus

4. Post-transplant lymphoproliferative disorders

5. Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

**Mechanism of pathogenesis**

In RA, 1) in the presence of autoreactive T cells of the specific clone, B cells producing autoantibodies such as the rheumatoid factor are activated; and 2) by immunosuppressive effects by MTX, the viral infection and reactivation of inapparent infection virus (especially, Epstein-Barr virus (EBV)) occur, and the clonal growth of B-cells is induced.

**Clinical observation**

In addition to systemic symptoms such as fever or weight loss, swelling of superficial and deep lymphnodes is found. Of the relatively lymphatic extranodal disease appear frequently, and it is reported that extranodal diseases such as skin, soft tissue and lung are relatively common [14]. Similar to the auditory cases of malignant lymphoma, increase of CRP, LDH and soluble interleukin-2 receptor (sIL-2R) is found in the laboratory data. When fever or lymphadenopathy is found in MTX-administered cases, this condition should be suspected, and a lymph node biopsy is usually performed.

**Imaging**

Similar to common malignant lymphoma, imaging shows lymphadenopathy and splenomegaly. Extranodal diseases of stomach, bones, eyes, bone marrow, pleura, lung, skin, thyroid gland and liver are reported [15]. Most of these are detected by CT; in addition, there is a report that FDG-PET contributes to the initial diagnosis and recurrence of MTX-LPD [16] (Fig. 9 on page 25).

**Treatment**

Treatment is to discontinue MTX immediately. Approximately 30% of cases are relieved within one month after MTX withdrawal, and it is reported that the regression rate is equal to approximately 60%, especially in EBV-positive cases [17]. MTX is discontinued, and follow-up is performed for two weeks. We just follow-up if in a tendency to regression, and chemotherapy is performed without a tendency to regression depending on histologic types. In addition, long-term follow-up is necessary because there is a report of case that recurred after the remission by MTX withdrawal. The repeated dose of MTX should be avoided [15].
9. Tamoxifen-induced uterine endometrial abnormality

**Concepts and Mechanism of pathogenesis**

Tamoxifen is one of the selective estrogen receptor modifiers, and has both of estrogen effects and antiestrogen effects. It is used for cases with breast cancer as postoperative chemotherapy or the treatment metastasis, because it mainly shows antiestrogen effects for the breast. In contrast it causes an influence such as the increase of uterus, regrowth of the uterine myoma and adenomyosis, increase in uterine cancer morbidity because it show estrogen effects for the uterus. The influence on endometrium varies as follows; atrophy, growth phase change, decidua-like change, endometrial polyp, endometrial hyperplasia, endometrial cancer. An increased risk of the uterine cancer is shown only in postmenopausal women: the hazard ratio rises to 2-3 times as compared with women of the same age, and it correlates with doses and dosing periods.

**Clinical observation**

When abnormal findings such as atypical genital bleeding or leukorrhea occurred in patients with internal use of tamoxifen, it is important to conduct a close inspection of the gynecology immediately.

**Imaging**

US and MRI can illustrate various changes in the uterus as stated above; especially MRI contributes to qualitative diagnosis (Fig. 10 on page 26). In tamoxifen-administered cases, endometrial polyps are common and the size of the uterus is often large [18].

10. Spinal compression fracture caused by chronic administration of steroid

**Concepts**

The adrenocorticosteroid is used for autoimmune disease such as rheumatoid arthritis or collagen disease, respiratory disease, renal disease and inflammatory bowel disease for the thanks of its anti-inflammatory action or immunosuppressive action. Osteoporosis is reported with the most in a steroid side effect, and it develops in 50% of long-term users for a steroid.

**Mechanism of pathogenesis**
The systemic therapy using the oral steroid medicine is closely associated with decreased bone quantity and the increased risk of fracture. The influence on bones begins within three months after the start of dosage, and show a peak in six months.

**Clinical observation**

The chief symptoms are swelling and pain of the fractured site. Often become the severe pain from early days. For the compression of spinal cord due to the fracture, a muscle weakness, stupor and bladder and rectal disturbance may rarely occur. Approximately one of three patients who broke a bone is reported to feel a severe pain in the back at a fracture. It is reported that the next fracture is easy to occur within one year when a single spine is fractured [19].

**Imaging**

An examination for bone mineral density using X-rays called DXA (dual-energy X-ray absorptiometry) is performed for the diagnosis of osteoporosis, and lumbar spine and proximal femoral head are commonly measured. Radiograph, CT, and MRI are used for the diagnosis of compression fracture of the spines. For the compression fracture, the front of the vertebral body is excluded, and the rear is preserved. So the upper endplate is depressed. In cases of osteoporosis, vertebral body may be flattened. On CT, fracture lines and sclerosis of superior facet of vertebral body are detected In addition to these findings. On MRI, the vertebra of fresh compression fracture presents a low signal intensity on T1-weighted image and a hyper intensity on T2-weighted image: these findings indicate the bone marrow edema. Also, the cavity including gas and the liquid is sometimes seen within the spines, indicating a fissure in vertebral body due to the osteonecrosis and the pseudoarthrosis, which often causes the protraction of the fracture healing and the algetic continuation.

**Treatment**

There are two treatments: conservative treatment and the surgical therapy. In recent years the minimum invasive therapy such as percutaneous vertebroplasty is established; excellent treatment effects for pain reliefs can be obtained (Fig. 11 on page 27).

**11. Internal anomalies in thalidomide embryopathy**

**Concepts**

Thalidomide was developed in 1954 by the German pharmaceutical company Grünenthal GmbH, and it was first marketed in 1957 in West Germany under the label of "Contergan"
and was subsequently licensed in 46 other countries. In 1961, the German pediatrician Widukind Lenz and the Australian obstetrician and gynecologist William McBride demonstrated that thalidomide has teratogenic effects, and it was then withdrawn from the market. It was estimated that there were more than 10,000 thalidomide babies all over the world. Recently several new cases of thalidomide embryopathy (TE) were reported in areas in Brazil that have a high prevalence of leprosy. It is well known that thalidomide causes severe limb defects including the well-publicized phocomelia, but it also causes various internal anomalies (IAs) such as IAs of the cardiovascular system, anomalies of the cranial nerves, the auditory organ and the gastrointestinal tract, some of which are fatal [20].

**Mechanism of pathogenesis**

Although over 30 hypotheses have been proposed regarding the teratogenic mechanisms of thalidomide, current research is concerned mostly with the following: Thalidomide binds to the protein Cereblon and inhibits the associated ubiquitin ligase activity. Then unknown substances are accumulated, and abnormalities occur in the signal transduction; the activity of the growth factor, fibroblast growth factor 8, is inhibited, and teratogenicity occurs (Fig. 12 on page 28).

**Clinical observation**

In the abdominal region, the lobulation anomaly of the liver, right-sided ligamentum teres hepatis, agenesis of the gallbladder, the urogenital organ such as vaginal atresia and the gastrointestinal tract. There have been reports that 23% of the patients with agenesis of the gallbladder have such symptoms as right upper abdominal pain, nausea and fatty food intolerance, and so on. In our institute, fusion of the left lobe and quadrate lobe of the liver were observed.

**Imaging**

These findings of TE are easily detectable by ultrasonography and CT. In general, patients with lobulation anomaly of the liver are reported to show intrahepatic bile duct and portal vein anomalies; in general, patients with lobulation anomaly of the liver are reported to show anomalies of intrahepatic bile duct and portal vein; such anomalies can be fully evaluated by unenhanced CT alone, however, detailed evaluation can be achieved using contrast-enhanced CT and MR cholangiopancreatography (MRCP) (Fig. 13 on page 29).
**Fig. 1:** An 88 year-old man hepatic biliary cyst (biloma) after TACE. In portal venous phase of contrast-enhanced CT 4 months after TACE (transcatheter arterial chemoembolization), dilatation of intrahepatic bile duct (arrow) distal to the treated hepatocellular carcinoma (T) and cystic structures (biloma) developed.

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Fig. 2: A 68 year-old man with supraumbilical skin rush in the anterior abdominal wall after the continuous intraarterial infusion chemotherapy of anticancer drug. A. Angiogram of the common hepatic artery. After intraarterial reservoir port placement after coil embolization for the hepatic falciform ligament artery (arrow) diverging from the left hepatic artery, the continuous arterial infusion chemotherapy for hepatocellular carcinoma was started. B. Photograph of anterior abdominal wall after 4 cycles of intraarterial infusion chemotherapy. Symmetric erythema developed in the anterior abdominal wall (arrowheads). Although we performed preventive measures as described, the recanalization of the coil-embolized portion of the hepatic falciform ligament artery due to thrombocytopenia caused the inflow of anticancer drug, resulting in the subcutaneous fat panniculitis. There was no relapse of clinical symptoms by additional embolization.

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Fig. 3: A 68 year-old man with blue liver following systemic chemotherapy using FOLFOX for liver metastases. Hepatobiliary phase of EOB-enhanced MRI shows decrease uptakes in the whole left lobe. A large defect in the right lobe is a liver metastasis (T).
Fig. 4: An 83 year-old woman with amiodarone liver. After long-term internal use of amiodarone for refractory ventricular arrhythmias. Unenhanced CT image. The attenuation of the hepatic parenchyma is diffusely increased (approximately 110HU); however, in this case, the level of the liver enzyme was not increased.

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Fig. 5: An 83 year-old man with multiple myeloma. During the treatment for multiple myeloma, his hepatobiliary enzymes rose and the levels were exacerbated. On T2-weighted MR image, a decrease in the signal intensity of both liver and spleen was shown, indicating hemosiderosis. Note the pleural effusion and ascites.

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Fig. 6: A 58 year-old man with NSAID ulcer. During chemotherapy using methotrexate and cylocide for central nerve recurrence of malignant lymphoma, he did sudden hematemesis. He concurrently had taken a steroid for a headache more than two months. The platelet count was 20,000 x 10^3/µL. A. Gastroscopy image. A gastric ulcer with active bleeding was detected in the gastric angle, we tried the hemostasis with the clip; however, the hemostasis was not achieved (arrow). B. Superselective angiography of the left gastric artery shows an extravasation (arrow) near the endoscopically placed clip. C. Superselective angiography of the left gastric artery show the disappearance of the extravasation after emobiling the bleeding branch through the microcatheter using microcoils. D. Gastroscopy image one week after TAE shows the stoppage of the bleeding and the ulcered lesion covered by fur.
Fig. 7: A 68 year-old woman with pseudomembranous colitis occurred during chemotherapy using cephem antibiotics of third generation. A. Contrast-enhanced CT shows diffuse wall thickening and dilatation of the colon (arrows). B. Colonic endoscopy shows the yellowish/grayish brown mucosa indicating pseudomembrane formation or necrosis.

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Fig. 8: A 78 year-old woman with biliary pseudolithiasis with the ceftriaxone Unenhanced CT image. Several hyperattenuated areas were shown in the gallbladder neck and cholecystic duct (arrows), which were disappeared on the follow-up CT; she was diagnosed biliary pseudolithiasis from the clinical course.

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Fig. 9: A 67 year-old man with methotrexate-related malignant lymphoma. A. Contrast-enhanced CT image shows enlarged retroperitoneal lymph nodes (arrows). B. Contrast-enhanced CT image shows some hypoattenuated masses (arrows) in the enlarged spleen. C. FDG-PET. Abnormal uptakes of FDG are shown, corresponding to the LNs and splenic masses (arrows).

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Fig. 10: An 83 year-old woman with uterine cancer that occurred after internal use of tamoxifen. Atypical genital bleeding developed after internal use with tamoxifen for four years for resected breast cancer. T2-weighted MR image. The endometrial cavity is filled with the hyperintense mass (arrows).

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Fig. 11: A 79 year-old woman with steroid-induced osteoporosis associated compression fracture in the thoracolumbar spines. Lumbago developed during long-term intake of prednisolone for rheumatoid arthritis and she couldn't get up afterwards. A-B. Sagittal section images of unenhanced CT. The bone mineral density in the thoracolumbar spines is decreased and the spines show a rough work in the whole, showing conditions of osteoporosis. In thoracic spine T12, height of vertebral body is decreased and gas-filled cleft is noted, indicating the finding of an unhealed compression fracture. On MRI (not presented), unhealed compression fracture in T11 is also shown. In addition, old compression fracture is shown in L1. We performed percutaneous vertebroplasty for thoracic spines, T11 and T12, and prompt pain relief was obtained (B).

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**Fig. 12:** Teratogenic mechanism of Cereblon binding

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**Fig. 13:** Fusion of the left lobe and quadrate lobe of the liver, seen in a 48 year-old man with thalidomide embryopathy. A-B. Unenhanced axial CT images of the abdomen show the hypoplasia of the fissure for ligamentum teres (arrows). In this case, the function and size of the liver was normal, and anomaly in the biliary system is not seen.

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Conclusion

1. In DVDs, radiologic imaging is useful in determining a severity of the disorder, searching the emergent cases and follow-up of the cases as well as the lesion detection.
2. Radiologists should recognize these characteristic findings to distinguish the DVDs from other benign or malignant conditions.
References


