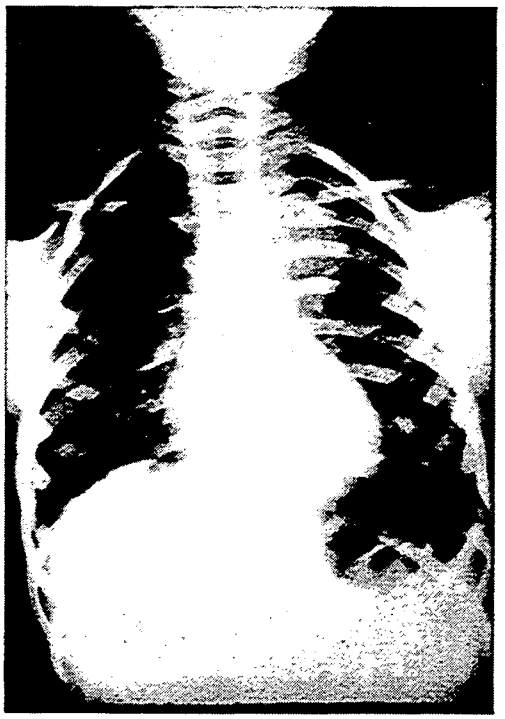


Figure 16.3: Skiagram chest outlining mediastinal deposits in a case of neuroblastoma

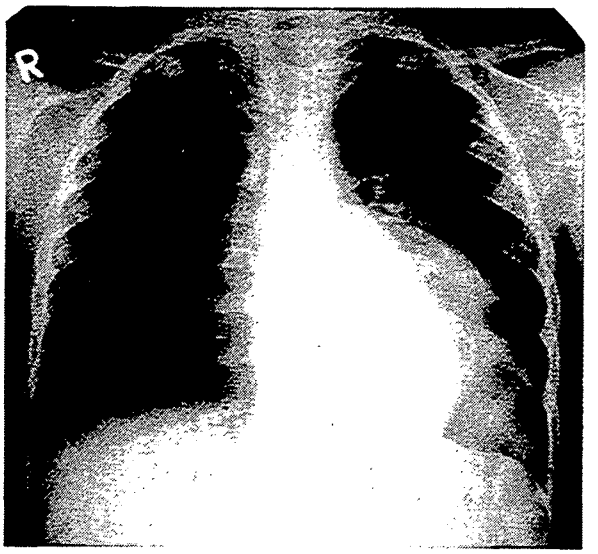


Figure 16.4: Skiagram chest showing a space occupying lesion in the left hemithorax that turned out to be a neuroblastoma of the posterior mediastinum

and metaiodobenzylguanidine (^{123}I MIBG) scintigraphy, if indicated. In Japan, neuroblastoma is not indicated in the application list of ^{123}I MIBG scintigraphy.

In the case of a thoracic neuroblastoma, imaging is 100 percent sensitive in suggesting the diagnosis[56] (Fig. 16.4). The mass is well defined and mediastinal based, associated with widening of the paraspinal line and rib erosion adjacent to the mass. On the other hand, plain abdominal radiography is less sensitive and often superfluous in terms of detection of the mass and intratumoral calcification. Thus the investigation should be followed with US regardless of the findings on abdominal radiograph.

On US, neuroblastoma is heterogeneously echogenic with poorly defined margins, and calcification, which is frequent, is identified as bright echoes with or without acoustic shadowing.[57] Most neuroblastomas demonstrate a "globular" region of increased echogenicity within the mass, which is regarded as an aggregate of uniform neuroblastoma cells marginated by reticulum and collagen.[58] The cystic form of neuroblastoma is rare, and located almost exclusively in the adrenal gland. This could be easily confused with adrenal hemorrhage as both have mainly been identified in neonates. Serial US imaging can resolve this problem as adrenal hemorrhage changes in its echo pattern and size over a period of days. Adrenal hemorrhage is rare *in utero* and any adrenal mass seen *in utero*, whether cystic or solid, is likely to be a neuroblastoma.[59] Careful US examination can demonstrate the origin and extent of the tumor, and the relationship of the tumor to the adjacent organs and major abdominal vessels. However, it is difficult to obtain or propose a convincing anatomic delineation for surgeons in planning surgery and predicting tumor resectability. Intravenous urography may show displayed renal calyces (Fig. 16.5).

Computed tomography (CT) is comparable to MR imaging as a cross-sectional imaging modality and both can demonstrate the presence and extent of neuroblastoma (Fig. 16.6). Although unenhanced CT is very sensitive in demonstrating intratumoral calcification and is advised for the evaluation of adjacent bones,[60] the additional information from MR imaging makes findings of less importance than was true previously (Figs 16.7A to C).

Because of its sensitivity to tissue characteristics and multiplanar and angiographic capability, MR has the advantage of distinguishing the tumor from other surrounding soft tissues, defining the tumor extent from the wide view or on any plane, showing its relationship to adjacent vessels without contrast medium, and demonstrating intraspinal spread, as well as accuracy in the recognition of bone marrow involvement (Figs 16.8A to C and 16.9).[61] There is a limitation, however, in

Figure 16.5: Intravenous urogram in a child with a huge neuroblastoma showing displayed renal calyces and vertebral anomalies

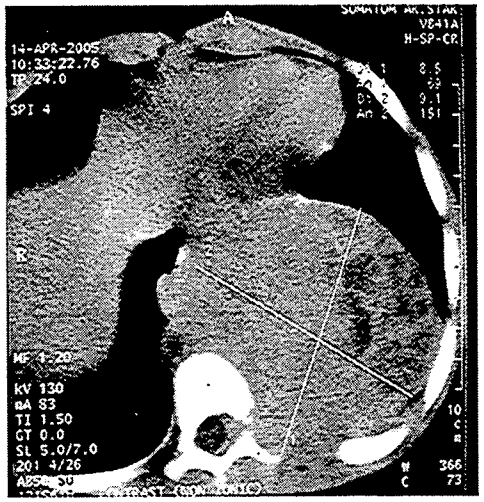


Figure 16.6: CT scan showing a posterior mediastinal neuroblastoma

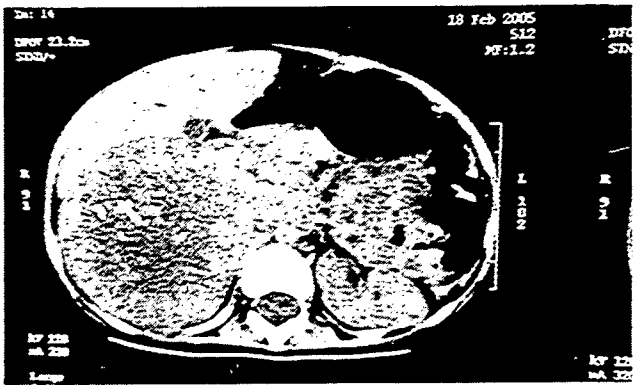


Figure 16.7A: Prechemotherapy CT scan image in axial section showing calcification in a case of neuroblastoma

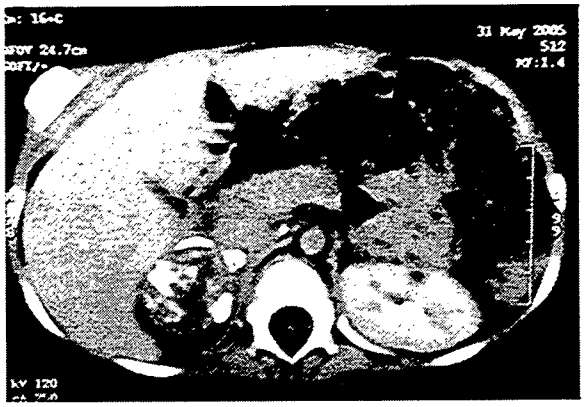


Figure 16.7B: Postchemotherapy CT scan image showing the residual tumor in axial section

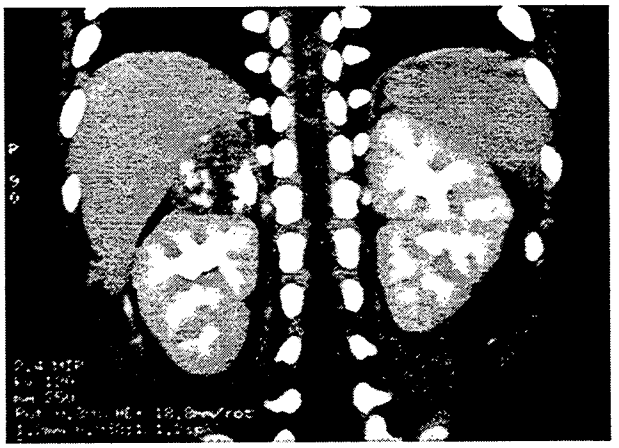
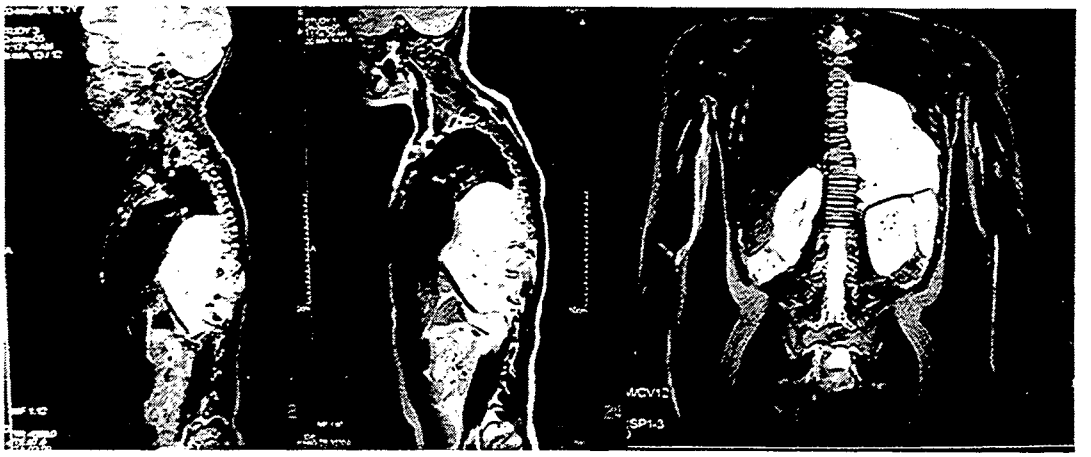


Figure 16.7C: Postchemotherapy CT scan image showing the residual tumor in coronal section

differentiating residual tumor from ongoing fibrosis or scar tissue after chemotherapy, and differential criteria remains to be established.

Bone scintigraphy with ^{99m}TC MDP is well established and more sensitive than radiographic bone survey for the diagnosis of skeletal metastases of neuroblastoma (Fig. 16.10). In addition, this radiotracer can accumulate in the tumor itself. MIBG scintigraphy is also able to detect primary tumor and metastases. As a positive finding on MIBG scintigraphy is more specific, it can



Figures 16.8A to C: MRI images in sagittal (**A** and **B**) and coronal sections **(C)** in a case of posterior mediastinal neuroblastoma with intraspinal extension

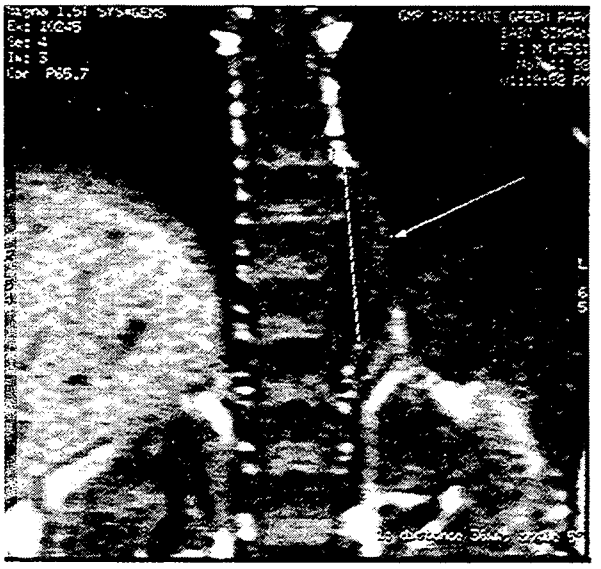


Figure 16.9: MRI image in coronal section showing a small mediastinal neuroblastoma

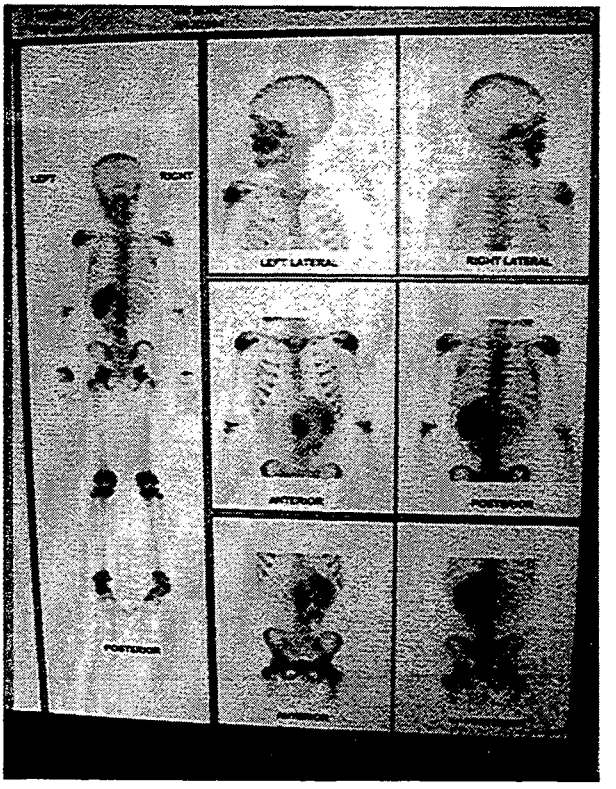


Figure 16.10: Bone scan images in a case of neuroblastoma showing thoracic and abdominal vertebrae involved with metastasis

noninvasively establish the diagnosis of neuroblastoma in a child with a tumor of unknown origin. Cumulative results of MIBG scintigraphy indicate that MIBG scintigraphy should be used initially, followed by bone scintigraphy, if necessary.[62]

TUMOR MARKERS

The implication of determining tumor markers is two-fold. One is to make a definitive diagnosis and monitor patients during the course of treatment, and the other is to predict prognosis. The most definitive diagnostic markers are catecholamines and their metabolites in serum and urine, although the positivity is approximately 75 to 80 percent in clinically diagnosed patients with neuroblastoma. Elevated neuron-specific enolase (NSE) levels are seen not only in the sera of patients with neuroblastoma but also in those with other pediatric tumors. However, serum NSE levels are elevated in all types of neuroblastoma whether or not the metabolic

pathways of catecholamines are present, and NSE serves as a good tumor marker in monitoring the disease course of neuroblastoma.[52,63]

A serum ferritin level > 142 ng/ml is found in many patients with advanced-stage neuroblastoma but rarely in low-stage disease, and it was reported that increased levels of ferritin are associated with a poorer progression-free survival rate.[64] Similarly, serum lactic dehydrogenase (LDH) levels > 1,500 U/ml are associated with a poorer prognosis in neuroblastoma,[65] and a serum NSE level elevated > 100 ng/ml is associated with poor survival in advanced-stage patients with neuroblastoma.[54]

The roles of CD44, ganglioside GD2, chromogranin A, neuropeptide Y (NPY), and proliferating cell nuclear antigen (PCNA) have been studied.[54] CD44 is a glycoprotein found in the cell surface of many tumors and is associated with aggressive behavior. Interestingly, expression of CD44 in neuroblastomas correlates with less aggressive behavior and has been highly predictive of favorable outcome.[66] Ganglioside GD2 is the characteristic ganglioside on human neuroblastoma cell membranes and increased plasma levels of GD2 have been found in patients with neuroblastoma. Shed ganglioside may accelerate tumor progression,[67] and human-type anti-GD2 monoclonal antibody combined with interleukin-2 is currently undergoing clinical trials in the United States.[68] Chromogranin A is an acidic protein present in the neurosecretary granules of neuroendocrine tumor cells, and has been identified as a marker possibly indicative of neuronal differentiation.[69] NPY is another neurosecretory protein, and its plasma levels may also indicate the level of neuronal differentiation in neuroblastoma.[70] PCNA correlates with the level of cell proliferation. The PCNA index in neuroblastoma is closely related to *MYCN* amplification and to poor prognosis.[71]

MASS SCREENING

The purpose of screening infants for neuroblastoma is to reduce the number of advanced-stage neuroblastomas in older children by identifying more number of infants with the favorable type of neuroblastoma. The concept of detecting catecholamine metabolites in urine dates back to LaBrosse, who first used spot tests of catecholamine metabolites for infants with neuroblastoma in 1968.[72,73] In 1972 Sawada started to screen infants for neuroblastoma in Kyoto using a quantitative vanillylmandelic (VMA) test (VMA spot test).[74] This test was changed to quantitative measurements of urinary VMA and homovanillic acid (HVA), mass screening of neuroblastoma was introduced in all prefectures in Japan in 1985, and the methods for the measurement of urinary VMA and HVA were refined to sensitive high-performance liquid chromatography (HPLC) in 1988.[75] As a result, the incidence of neuroblastoma changed after the introduction of nationwide mass screening. Between 1980 and 1985, approximately 120 patients with neuroblastoma were registered yearly, while the number of annual neuroblastoma patients increased to about 250 during the period from 1991 to 1995.[2,75] Neuroblastomas identified in infancy through mass screening were exclusively of the favorable types, and roughly 99 percent of such infants have been cured, some of whom were only observed.

It must be remembered that the purpose of mass screening is to decrease the number of older children with advanced neuroblastoma. Some questions have been raised in this respect,[76] and it was shown that the absolute number of stage IV (excluding stage IV-S) neuroblastoma patients older than 12 months of age was not decreasing significantly when the number of live births was taken into account (Table 16.2).[2] Not all neuroblastoma, perhaps only 75 to 80 percent, possess the metabolic pathways of catecholamines.[11] Overdiagnosis of infant neuroblastoma which otherwise might have regressed spontaneously has also been pointed out.[76,77] A consensus conference to discuss the true value of mass screening was held in Lyon, France, in December 1998. Investigators from North America reported that they were negative toward mass screening based upon their own data,[77] and the majority of European researchers agreed with the contention of the North American group,[78] but the German group emphasized that one must consider the results of the German mass screening conducted at the age of 12 months[79] and which may reduce overdiagnosis of infant neuroblastoma.

TREATMENT OF LOW-RISK NEUROBLASTOMA

The treatment of neuroblastoma should be planned individually according to the risk group. There has been argument over whether neuroblastoma consists of two or three types of tumor. Brodeur and Ambros[41] consider that it consists of three types, low risk (type 1), intermediate risk (type 2A), and high risk (type 2B), but the differentiation between their type 2A and type 2B is difficult from a clinical viewpoint, and it should be

Table 16.2: The incidence of stage IV neuroblastoma in Japan, according to Tsuchida et al[2]

Year	Number of neuroblastoma cases*	Number of stage IV neuroblastoma patients older than 12 months of age	Number of live births
1981	107 (1)	55	1,529,455
1982	139 (4)	63	1,515,392
1983	152 (8)	62	1,508,687
1984	136 (12)	46	1,489,780
1985	142 (32)	40	1,431,577
1986	162 (39)	56	1,382,946
1987	143 (49)	30	1,346,658
1988	198 (88)	57	1,314,006
1989	179 (90)	33	1,246,802
1990	190 (108)	40	1,221,585
1991	238 (138)	51	1,223,245
1992	229 (121)	54	1,208,989
1993	207 (135)	32	1,188,282
1994	298 (208)	41	1,238,328
1995	222 (140)	32	1,187,064
1996	238 (162)	28	1,206,555
1997	276 (164)	47	1,191,665
1998	229 (147)	29	1,203,147

*Numbers in parentheses represent cases identified by mass screening and are part of the total. Cases with incomplete data with regard to patient age and disease stage are excluded.[61]

taken into account that prognosis is not determined by *MYCN* amplification alone. Therefore, division into two types, as proposed by Tsuchida and La Quaglia,[80] appears to be more reasonable (Table 16.3).

Low-risk neuroblastomas here denote those occurring in infants younger than 12 months of age in INSS stage I, II, III, and IV-S and without *MYCN* amplification. These tumors should be treated less intensively compared with high-risk tumors.[81] Some neuroblastomas found by mass screening at about 6 or 7 months of age may be treated by observation only if the mass is less than 3 to 4 cm in diameter and does not show any signs of enlargement during the observation period.[82] Nevertheless, in the majority of institutions, the tumor is excised and less aggressive surgery is recommended.[83] Original tumors in stage I, II, and IV-S are excised at the start of treatment, but they should be removed after chemotherapy when they are in stage III.

Chemotherapy for low-risk neuroblastoma should not be aggressive. In Japan, no chemotherapy is administered for stage I and II tumors after complete resection. The recommended preoperative chemotherapy for infant neuroblastoma in stage III consists of alternating weekly administration of vincristine 1.5 mg/m^2 iv and cyclophosphamide 300 mg/m^2 iv, repeated six times. For stage IV without bone cortex metastases, regimen C2 consisting of vincristine 1.5 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1 and pirarubicin (THP-adriamycin, Nihon Kayaku, Tokyo) 30 mg/m^2 on day 3 is given nine times at 4-week intervals.[81]

When the tumor is associated with *MYCN* amplification and/or 1p-deletion and/or bone cortex metastases, the infants are treated with a modification of the regimens for advanced neuroblastoma.

TREATMENT OF HIGH-RISK NEUROBLASTOMA

High-risk neuroblastomas here denote those occurring in children older than 12 months of age, in INSS stage III and IV, and with/without *MYCN* amplification. Reports[84,85] show that the results of treatment of stage III and IV disease in older children are still not very good, and are poorer when associated with *MYCN* amplification. Yet it is generally agreed that these two groups, *MYCN* amplified and unamplified, should be given the same consideration as high-risk neuroblastoma. The prognostic significance of *MYCN* amplification is very clear in low-stage patients, but not as clear in stage IV patients.[42,85,86] In the treatment of high-risk neuroblastoma, chemotherapy is vitally important.

Table 16.3: A simplified comparison of risk factors for high- and low-risk neuroblastoma by Tsuchida and La Quaglia[80]

Parameter	*High-risk*	*Low-risk*
Age	> 1 year, especially > 2 years	< 1 year
Stage	INSS IV, some III	INSS I, II, III, IV-S
MYCN status	> 10 copies	9 copies, especially < 3 copies
1p36 deletion	Present	Absent
Shimada classification	Unfavorable	Favorable
Ploidy	Diploid	Hyperploid
Trk-A expression	Absent	Present
Ferritin at diagnosis	> 143-150 ng/ml	< 143-150 ng/ml

Chemotherapy

Numerous chemotherapeutic protocols have been proposed and utilized worldwide for advanced neuroblastoma.[86]

Different induction chemotherapeutic regimens were used in Japan from March 1991 to May 1998 based on *MYCN* amplification status (Table 16.4).[87] Researchers were requested to perform a biopsy before treatment and to treat all stage IV patients with one cycle of regimen new A_1 while awaiting the results of Southern blot analysis of the *MYCN* oncogene. When the tumor was found to contain more than 10 copies of *MYCN*, patients received five courses of regimen A_3 until a total of six cycles was reached. On the other hand, if it was found to contain fewer than 9 copies of *MYCN*, patients received further courses of regimen new A_1 until a total six cycles was reached. Both regimen new A_1 and regimen A_3 were well tolerated with acceptable complications.[87] Matthay and her associates used an induction chemotherapeutic regimen similar to this (Table 16.4),[88] but they used a single regimen for both *MYCN*-amplified and unamplified neuroblastomas.

Table 16.4: Induction chemotherapy regimens (Kaneko et al. from 1991 to 1998[87])

Regimen new A_1
- Cyclophosphamide 1,200 mg/m^2 day 1
- THP-adriamycin 40 mg/m^2 day 3
- Etoposide 100 mg/m^2/day days 1, 2, 3, 4, 5
- Cisplatin 90 mg/m^2 day 5

Regimen A_3
- Cyclophosphamide 1,200 mg/m^2/day days 1, 2
- THP-adriamycin 40 mg/m^2 day 3
- Etoposide 100 mg/m^2/day days 1, 2, 3, 4, 5
- Cisplatin 25 mg/m^2/day days 1, 2, 3, 4, 5 (continuous)

Matthay et al from 1991 to 1996[88]

Regimen
- Cisplatin 60 mg/m^2 day 1
- Adriamycin 30 mg/m^2 day 3
- Etoposide 100 mg/m^2/day days 3, 6
- Cyclophosphamide 1,200 mg/m^2/day days 4, 5

Surgery

Radical surgery is performed during the first six cycles of induction chemotherapy. It seems ideal to operate after the fourth or fifth cycle of intensive induction chemotherapy. There are some controversies regarding the timing of surgery, operative methods, and value of surgical resection in high-risk neuroblastoma.[80]

Excision of the primary tumor and retroperitoneal lymph node dissection are carried out systematically in the six sections defined by the authors, as shown in Figure 16.11.[89] These include areas to the left of the abdominal aorta (1+2); between the aorta and vena cava (3+4); and to the right of the vena cava (5+6); with further subdivision according to the level of the renal vein. When the tumor occurs on the left, dissection begins at the common iliac lymph nodes and moves upward after exploring the left common or external iliac artery and dissecting its adventitia longitudinally along the middle (section 1). During this process, neuroblastoma in the left adrenal gland is removed, but every effort should be made to preserve the left kidney.

The inferior and superior mesenteric arteries and the celiac axis are encountered in that order during dissection. Lymph nodes located on the right side of these arteries are not removed at this time, but are left in place for the following step. During dissection, care is taken not to damage the left renal artery and its adventitia; dissection stops at the outer sheath and a small sponge soaked in procaine chloride is left in place during the procedure. Next, the dissection proceeds to the suprarenal region (section 2).

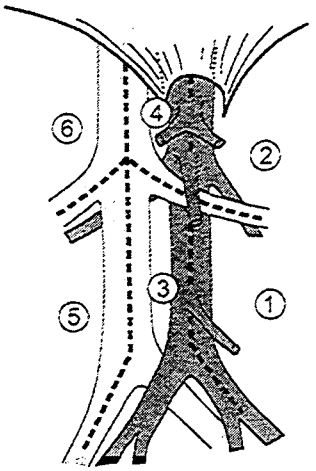


Figure 16.11: Retroperitoneal lymph nodes divided into six sections [80,89]

Dissection of the infrarenal lymph nodes located between the aorta and the vena cava (section 3) is also carried out from the left side. It begins at the level of the aortic bifurcation and moves upward. This dissection can commence from the right side when the tumor originates on that side, and the right retroperitoneal space is entered first, after deflecting the ascending colon and duodenum. Dissection of the suprarenal lymph nodes between the aorta and the vena cava (section 4) is accomplished during the final stage of the surgery.

To facilitate dissection of the infrarenal lymph nodes to the right of the vena cava (section 5), the ascending colon and the duodenum are now deflected to the midline. Dissection of section 5 begins from the right common iliac lymph nodes upward and is completed at the level of the right renal vein. After mobilizing the right lobe of the liver, the right suprarenal lymph nodes (section 6) are dissected up to the insertion of the right diaphragm.[80,89]

Miyauchi and coworkers confirmed histologically that removal of the contralateral retroperitoneal lymph node is mandatory in advanced neuroblastoma.[90] In 12 patients in whom neuroblastoma originated on the left side, metastases were found histologically in the lymph nodes lateral to the aorta (sections 1+2) in all. In the lymph nodes between the aorta and the vena cava (sections 3+4) metastases were positive 11 of the 12, while in the lymph nodes lateral to the vena cava (sections 5+6) one of 7 contained neuroblastoma (Table 16.5). In 5 patients with a right-sided neuroblastoma, all the lymph nodes lateral to the vena cava (sections 5+6) and between the vena cava and the aorta (sections 3+4) had histological evidence of metastases. In addition, four of the five had metastases in the lymph nodes lateral to the aorta (sections 1+2) (Table 16.5).[90]

Patients who undergo radical excision of primary tumor and retroperitoneal lymph nodes should be managed carefully during the postoperative period.

The value of surgical resection in high-risk neuroblastoma is not great. Although the authors have confirmed its value statistically,[91] it should be kept in mind that radical surgery only minimizes the incidence of local recurrence after intensive treatment including autologous bone marrow transplantation (ABMT).[92] The low incidence of local recurrence was previously verified in the authors' series, because local recurrence has been encountered very rarely.

Radiation

Neuroblastoma is radiosensitive.[93] Local recurrence of a primary high-risk neuroblastoma is decreased by radiotherapy to the site (25-30 Gy) to the site, particularly when high-dose chemotherapy is also administered.[94] Total body irradiation may be used prior to autologous bone marrow transplantation, but is not used by some institutions.

Intraoperative radiation therapy has advantages over conventional external irradiation because all necessary doses are delivered to the tumor bed at one time only.[95] However, the radiation field of intraoperative irradiation is usually smaller than that in conventional external irradiation.[89]

Table 16.5: Lymph node metastases identified at radical surgery[90]

Primar tumor occurring on the right side (5 patients) Positive metastases in lymph nodes			*Primary tumor occurring on the left side (12 patients) Positive metastases in lymph nodes*		
Right	*Middle*	*Left*	*Right*	*Middle*	*Left*
5/5	5/5	4/5	1/7	11/12	12/12

Right refers to nodes lateral to the vena cava; middle refers to nodes between the vena cava and aorta; and left refers to nodes lateral to the abdominal aorta.

Bone Marrow Transplantation

The safety of ABMT is increased by purging tumor cells from the harvested marrow with the use of immunobeads coupled with monoclonal antibodies.[96] Allogeneic transplantation does not require purging but strict immunologic compatibility between graft and host must be present, and therefore this is not used widely. The effects of ABMT have been confirmed and were reported by Matthay and her associates.[88] It should be remembered that ABMT is effective only when complete remission (CR) or near CR is achieved with high-dose induction chemotherapy and surgery.[97] Some institutions use tandem ABMT, but its value over conventional ABMT has not yet been confirmed.

Results of Treatment of High-risk Neuroblastoma

Not all patients with high-risk neuroblastoma will die, even though their tumors have more than 10 copies of *MYCN*. From January 1985 to September 1993, 66 patients with neuroblastoma containing more than 10 copies of *MYCN* were treated in the Study Group of Japan. Five of 9 patients with stage III disease, 13 of 55 with stage IV, and one of II with stage IV-S survived for at least 66 months. It is interesting that all but one patient who survived for more than 66 months underwent ABMT. In total, 19 (28.8%) of 66 patients were long-term survivors for more than 66 months.[98] Further improvement in treatment results is expected.

NEW THERAPY

MIBG Treatment

Both ^{125}I and ^{131}I-MIBG are reported to be effective against high-risk neuroblastoma.[99,100] Preoperative treatment of stage III or IV tumors with ^{131}I-MIBG resulted in a 95 percent reduction in tumor size in more than 50 percent of patients with minimal toxicity; only 20 percent showed no appreciable change.[101] It appears that preoperative radioactive MIBG treatment may be equal to induction chemotherapy with less toxicity. The use of MIBG is, however, not widespread in the United States and Japan.

New Agents

Irinotecan (CPT-11) is a new agent for the treatment of high-risk neuroblastoma. So far, phase I clinical trials have been completed in the United States, France, and Japan.[102,103] Inclusion of human endostatin in the treatment of high-risk neuroblastoma is expected[104] as well as that of TNP-470, a synthetic analogue of a natural product of *Aspergillus fumigatus*.[105,106]

LATE EFFECTS AND SECOND MALIGNANCIES

Meadows and Tsunematsu reported that the late effects of treatment of high-risk neuroblastoma are not significant. They reported that 19 of 790 patients with neuroblastoma developed a second malignancy; 7 of the 19 developed carcinoma of the thyroid. In the Japanese Childhood Second Leukemia Registry, 15 of 98 cases occurred in neuroblastoma survivors. However, the incidence of secondary leukemia is thought to be low.[107]

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低リスクA群は標準的なVAC療法(ビンクリスチン, アクチノマイシンD, シクロホスファミド)を21週投与, 低リスクB群は強化VAC療法(シクロホスファミドを増量)を21週投与し, さらにVA療法を45週まで投与する。中間リスク群では強化VAC療法を39週投与する。高リスク群に対しては強化VAC療法を推奨しているが予後不良であるため, JRSGでは施設限定で強化寛解導入療法に大量化学療法＋自家造血幹細胞移植を行う多施設共同研究が開始されている。またIRS-Vでは強化VAC療法にイリノテカンの併用が試みられている。

6 予後

治療法の進歩により治療成績は改善し, IRS-Ⅲ(1984-1991年)では5年生存率は71%, 5年progression free survival(PFS)は65%となっている。Group以外の予後因子として組織型, 発生部位, 病期, および年齢があるが, これらを加味したリスク分類によりIRS-Ⅲ,Ⅳの治療成績を示す。

a) 低リスクA群およびB群

①胎児型GroupⅠ-ⅡでStage 1-3(すべての部位)/症例, ②胎児型GroupⅢでStage 1(予後良好部位)/症例がこの群に属する。5年生存率は78～100%と良好である。

b) 中間リスク群

①胎児型GroupⅢでStage 2, 3(予後不良部位), 症例, ②胞巣型GroupⅠ-ⅢでStage 1(予後良好部位), 症例, ③胞巣型GroupⅠ-ⅡでStage 2-3(予後良好部位), 症例が中間リスク群である。強化VAC療法＋放射線治療＋手術で5年生存率は72～80%である。

c) 高リスク群

①胞巣型GroupⅢでStage 2-3(予後良好部位)症例, ②すべてのGroupⅣ Stage 4症例がこの群に含まれる。5年生存率は50%である。特に胞巣型でStage 4／GroupⅣ症例は5年生存率30%と最も予後不良である。

今後, JRSGにより胞巣型症例, 遠隔転移症例の治療成績改善が期待される。

7 悪性リンパ腫

学習のポイント

- 悪性リンパ腫は非Hodgkinリンパ腫とHodgkin病に大別される。
- 日本では欧米と異なりHodgkin病が少ない。Hodgkin病の頻度は小児悪性リンパ腫の10%程度である。
- 腹部の悪性リンパ腫は腸重積, 消化管出血, 穿孔, 通過障害, 閉塞性黄疸などの原因となる。
- Hodgkin病は頚部や鎖骨上窩の無痛性リンパ節腫大として発症することが多い。

1 非Hodgkinリンパ腫 non-Hodgkin lymphoma

a) 分類・病態

小児非Hodgkinリンパ腫の大部分はびまん性リンパ腫で, リンパ芽球型, バーキット(Burkitt)型, 大細胞型などに分類され, リンパ芽球型とバーキット型の頻度が高い。リンパ芽球型は主にT細胞型で前縦隔に発生することが多い。B細胞由来のバーキット型リンパ腫はリンパ節外性発症が多く消化管, 後腹膜, 扁桃などに好発する。組織学的にはstarry-sky appearance(星空様の所見)が特徴的で, 免疫グロブリンIgM, 表面抗原CD19, CD20などを発現する。大細胞型はB細胞またはT細胞由来であるが, 未分化大細胞型リンパ腫(anaplastic large cell lymphoma)はKi-1抗原(CD30)陽性であり, 近年では独立した病態として扱われている。

腹部に原発した悪性リンパ腫は腸重積のほか, 消化管の出血, 穿孔や通過障害, 閉塞性黄疸などの原因となり, 腹痛, 腹部腫瘤, 嘔吐, 黄疸などの症状を呈する(図19-28)。特に回盲部に原発した症例では虫垂炎や虫垂炎に伴う膿瘍形成と紛らわしい例があり注意が必要である。消化管に浸潤した症例では治療中に消化管穿孔や出血を起こす

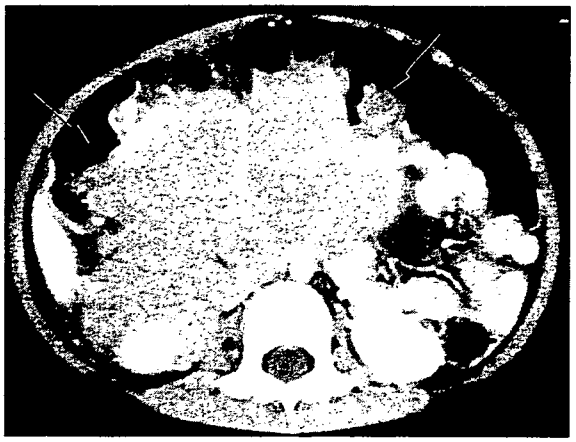

図 19-28　腹部原発非 Hodgkin リンパ腫(B 細胞，大細胞型)
腹部腫瘤で発症(矢印)

ことがある。

胸部原発の場合には前縦隔腫瘍として発見される。

b) 診断・病期

臨床的に悪性リンパ腫が疑われたら，CT，MRI，骨シンチなどに加え Ga シンチ，骨髄検査，髄液検査などを行う。血中 LDH は高値を示すことが多い。血中の可溶性 IL-2 受容体は非 Hodgkin リンパ腫の腫瘍マーカーとされるが T 細胞との関連が深い。生検による組織学的検索と表面マーカー，染色体分析，遺伝子検索などにより確定診断を得る。病期分類は Murphy の分類が用いられる(表 19-10)。

表 19-10　Murphy の病期分類

Ⅰ	節外性病変では単独の腫瘤。リンパ組織病変では 1 リンパ領域。 縦隔，腹部原発を除く。
Ⅱ	節外性で限局性病変で所属リンパ節転移を伴う。 横隔膜の同側の病変　①二つの節外病変 ②二つ以上のリンパ節領域に及ぶ病変 原発性消化管腫瘤(大部分は回盲部)でリンパ節転移を認めないか，所属リンパ節病変にとどまるもの。かつほぼ完全に切除されたもの。
Ⅲ	節外性で横隔膜の両側にある限局性病変。 横隔膜の両側にある二つ以上のリンパ節領域に及ぶ病変。 すべての胸腔内原発腫瘤(縦隔，胸膜，胸腺)。 すべての腹腔原発の進行性病変。 腫瘍の原発部位とは関係なく，すべての脊髄周囲あるいは硬膜外病変。
Ⅳ	中枢神経または骨髄転移，あるいはその両方を伴うもの。

加藤忠明(監修)：小児慢性疾患診療マニュアル．診断と治療社，2006 より引用

c) 治療・予後

診断が確定した後に組織型に応じた多剤併用化学療法を行う。悪性リンパ腫は早急に化学療法を開始する必要のある全身疾患であることを理解し，たとえ腹部腫瘤で開腹したとしても悪性リンパ腫の術中診断が得られたら原発巣切除の適応はない。検索に必要な組織採取のみを行い閉腹する。骨髄，胸水，腹水の細胞診や，転移リンパ節の生検で診断できれば開胸や開腹による組織採取の必要はない。ただし消化管に限局した病変や，腸重積，消化管穿孔，出血などで緊急開腹となった場合には消化管の部分切除による病変の切除を行う。

非 Hodgkin リンパ腫では腫瘍は急激に増殖し，細胞回転が速く大量の腫瘍細胞が細胞死に至るため，高尿酸血症や電解質異常，腎障害をきたすことがある。これを腫瘍溶解症候群(tumor lysis syndrome)という。化学療法の際には尿酸産生抑制薬アロプリノールの投与や十分な輸液，尿のアルカリ化などの処置を行うが，周術期の管理の際にも注意が必要である。

非 Hodgkin リンパ腫では進行例でも 70～80%の生存率が期待できる。

2 Hodgkin 病 Hodgkin disease

Hodgkin 病は頚部や鎖骨上窩の無痛性リンパ節腫大として発症することが多い。5 歳以下の発症は稀である。縦隔へ進展し，発熱，倦怠感，体重減少，夜間の発汗などの症状を伴う。最も大きいリンパ節を生検し，診断を確定する。組織学的には Hodgkin 細胞と特徴的な Reed-Sternberg 細胞が観察され，リンパ球優勢型(lymphocyte predominance)，結節硬化型(nodular sclerosis)，混合細胞型(mixed cellularity)，リンパ球減少型(lymphocyte depletion)の 4 型に分類される。わが国の小児 Hodgkin 病では混合細胞型が最も多く約半数を占めている。

表 19-11 Cotswolds の分類(1989 年)

病 期	定 義
Ⅰ期	1つのリンパ節領域に限定された病変
Ⅱ期	横隔膜の一側で2つ以上のリンパ節領域に病変が存在する 縦隔は1つの部位として算定し，肺門部は左右別々に算定する 病変が存在する部位の数を位置を下げた小さな字で記載する
Ⅲ期	横隔膜の両側のリンパ節領域に病変が存在する
Ⅲ1期	脾，脾門部リンパ節，腹腔リンパ節，門脈リンパ節に病変が存在する
Ⅲ2期	大動脈周囲リンパ節，腸骨リンパ節，腸間膜リンパ節に病変が存在する
Ⅳ期	病変リンパ節に連続または近接した複数の節外臓器に病変が存在する あるいは遠隔節外臓器に病変が存在する

赤塚順一，他(編)：小児がん．医薬ジャーナル社，2000

病期分類には Cotswolds の分類が用いられる(表 19-11)。病期診断を目的とした開腹(staging laparotomy)は放射線照射のみで治療を行う例や開腹の結果で照射野に変更が生じる例など，その適応は限られている。

治療は化学療法が主体であり必要に応じて放射線照射を併用することが多く，早期例で 90%以上，進行例で 80～90%の生存率が得られている。

8 血管腫

学習のポイント

- 小児の血管病変は血管腫と血管奇形に分類される。
- 血管腫は内皮細胞の増殖を伴い，増大した後に退縮する病変で，女児に多い。
- 有症状または合併症を伴う血管腫は積極的な治療の対象となる。
- 血管奇形は内皮細胞の増殖を伴わない血管の発生異常で，退縮することはない。また，頻度に性差はない。

小児血管病変の分類(表 19-12)

これまで小児の血管腫と総称される病変には病因や病態の異なるさまざまな血管病変が含まれ，その理解を困難なものとしていた。1982 年，Mulliken & Glowacki は自然経過と組織学的所見をもとに血管病変を腫瘍性の血管腫と非腫瘍性の血管奇形に分類することを提唱した。近年，この分類をもとに小児の血管病変が再分類，整理されており，病因や病態に基づいた病変の理解が可能

表 19-12 小児の血管病変

Ⅰ	血管腫(hemangioma, hemangioma of infancy)
	増殖期(proliferating phase)
	退縮期(involuting phase)
Ⅱ	血管奇形(vascular malformation)
	毛細血管奇形(capillary malformation)
	静脈奇形(venous malformation)
	動静脈奇形(arteriovenous malformation)
	動静脈瘻(arteriovenous fistula)
Ⅲ	その他の血管病変
	正中母斑(サーモンパッチ)(macular stain, salmon patch)
	先天性血管腫(congenital hemangioma)
	カポジ型血管内皮腫(Kaposiform hemangioendothelioma)
	房状血管腫(tufted angioma, angioblastoma)
	化膿性肉芽腫(pyogenic granuloma)

になった。しかし小児の血管病変を正しく診断し，適切に治療するためには，これまでの記述的分類を含めた包括的な理解が必要である。

2 血管腫 hemangioma, hemangioma of infancy

a) 症状・診断

血管腫は内皮細胞の増殖を伴い，増大した後に退縮(縮小)する病変である。40%では生下時に皮膚に紅斑や斑状出血，紅色丘疹，毛細血管拡張などがみられる。血管腫は生後3か月頃までに明らかとなり，数か月間は急速に増大するが，その後，徐々に退縮し多くは就学前に消失する(図19-29)。退縮後に腫瘤，皮膚のたるみ，毛細血管拡張，瘢痕などを残すことがある。退縮期には内皮細胞が減少し，線維組織や脂肪に置換される。血管腫の増大および退縮には複数の血管新生調節因子が関与すると考えられているが，その詳細な機序は不明である。

血管腫は女児に多く，早産や低出生体重がリスクとされている。頭頸部にみられることが多く，多発することもある。皮膚の血管腫はイチゴを割って置いたような外観から苺状血管腫(strawberry hemangioma)と呼ばれ，潰瘍形成や感染を合併することがある。深部臓器にも発生し，唾液腺，眼窩，喉頭(声門下)の血管腫はそれぞれ外耳道閉塞，視覚障害，呼吸障害の原因となる。肝の血管腫では動静脈シャントによる高拍出量が原因でうっ血性心不全をきたすことがある。腫瘍内における血小板消費による血小板減少と出血傾向をKasabach-Merritt症候群(現象)と呼び，血管腫で稀にみられるとされてきた。しかし，近年，同現象は血管腫よりも後述のカポジ型血管内皮腫や房状血管腫と関連するものと理解されている。

診断は多くの場合，経過と理学的所見により可能であるが，深部の血管腫では超音波検査，CT，MRIなどが有用である。特にMRIではT1強調像で筋肉と等信号または低信号，T2強調像で高信号の充実性腫瘤として描出され，腫瘤内の血流をflow voidとして捉えることができる(図19-30)。

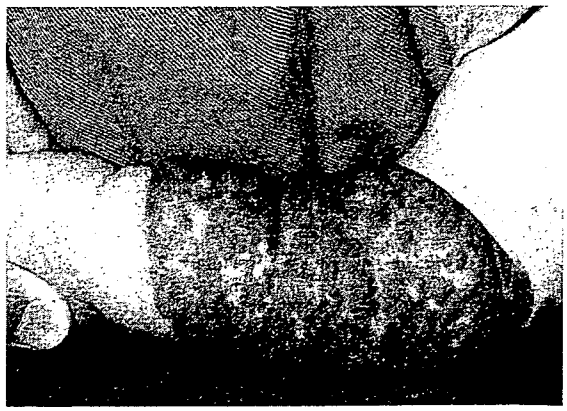

図19-29　血管腫の外観

b) 治療

自然退縮を待つことを原則とするが，視覚障害，呼吸障害，心不全，Kasabach-Merritt症候群などの原因になる場合や，潰瘍形成，出血を伴う場合には治療を行う。ステロイドの内服やインターフェロン-αの全身投与が有効で，ステロイドは30%で退縮を促進する。一方，インターフェロン-αでは副作用として神経麻痺の報告があり，ビンクリスチンやサイクロフォスファマイドの有効性も示されている。表在性の血管腫に対してはレーザー治療が有効で，これらの治療に反応しない場合や，特に肝の血管腫では塞栓術や動脈結紮術，切除などが行われる。また，小線量の放射線も有効である。

3 血管奇形 vascular malformation

a) 症状・診断

血管奇形は内皮細胞の増殖を伴わない血管の発生異常で，生下時に存在し，児の成長に比例し増大するが退縮しない。血管腫と異なり，頻度に性差はない。血管奇形は血管と血流の性状により低流量の毛細血管奇形(capillary malformation)，静脈奇形(venous malformation)，高流量の動静脈奇形(arteriovenous malformation)，動静脈瘻などに分類される。

毛細血管奇形はポートワイン母斑(port wine stain)や単純性血管腫と呼ばれ，赤ワイン様の色調を呈し，皮膚から隆起しない局面で圧迫により退色する(図19-31)。生下時から存在し，自然には消退しない。三叉神経領域にみられるものをSturge-Weber症候群という。

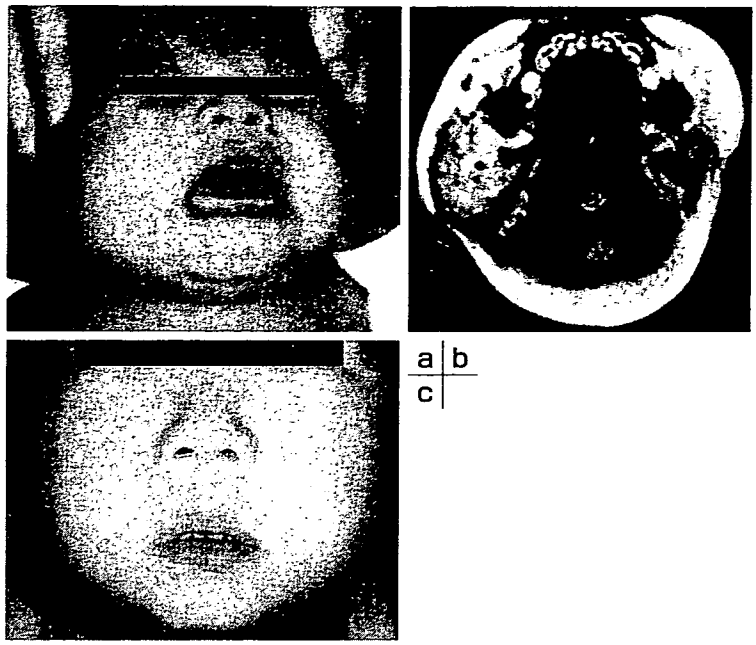

図 19-30 右耳下腺血管腫(女児，生後 1 か月，頬部の腫脹で発症)
a：生後 2 か月の外観，b：MRI(T 2 強調像で高信号，flow void を認める)，c：2 歳時の外観(自然退縮後)

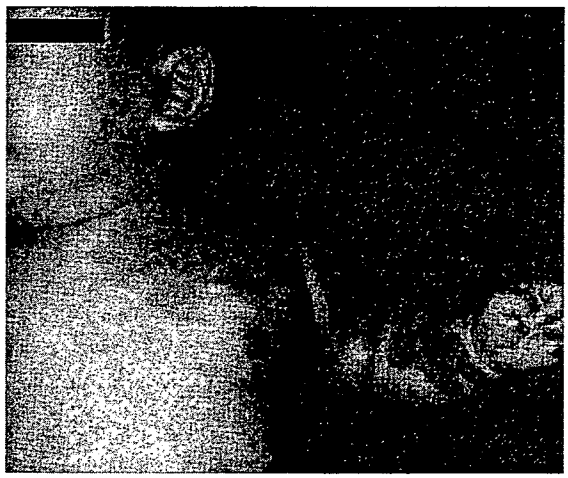

図 19-31 毛細血管奇形(単純性血管腫)

静脈奇形は海綿状血管腫(cavernous hemangioma)と呼ばれてきた病変で，全身のいずれの部位にも認めうる。皮下にある場合は淡青色を呈する弾性軟の腫瘤として触知し，圧迫により縮小する特徴(圧縮性)がある。

動静脈奇形は生下時から存在するが，思春期とともに，あるいは外傷を契機に増大し発症することがある。皮下の病変では患部は暖かく，血管性の拍動(thrill)を触知し，血流を血管性雑音(bruit)として聴取するなどの特徴がある。

診断には MRI が有用で，静脈奇形では T2 強調像で高信号の病変として描出され，円形の静脈結石が描出されることもある。

b) 治療

毛細血管奇形ではレーザー治療が用いられる。静脈奇形は切除の対象となるが，局所の圧迫も有効で，硬化療法の報告もある。動静脈奇形も切除の対象となるが，切除困難な場合には選択的な動脈塞栓術が行われる。

その他の血管病変

a) 正中母斑(サーモンパッチ)macular stain (salmon patch)

Angel's kiss(天使のキスマーク)，stork bite(コウノトリがくわえた跡)とも呼ばれる。淡紅色を呈し扁平で，圧迫により退色する。眉間，眼瞼，前額，頚部にみられ，特に項部にあるものをウンナ母斑という。多くは幼児期に消退する(図 19-32)。

b) 腫瘍

先天性血管腫(congenital hemangioma)は胎内で増殖期を迎え，生下時にはすでに増大した病変として存在する(図 19-33)。出生後に増殖期に入る通常の血管腫との異同は不明であるが，退縮す

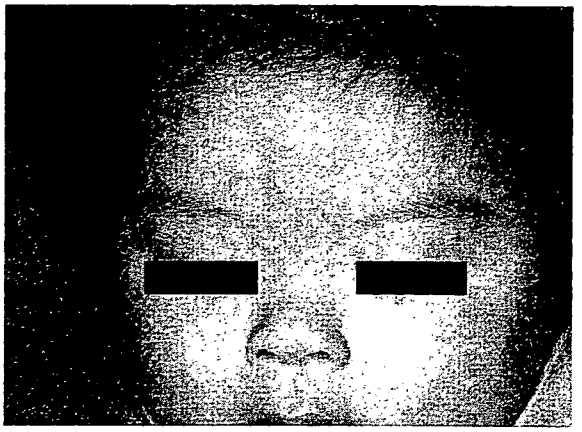

図 19-32　正中母斑(前額部)

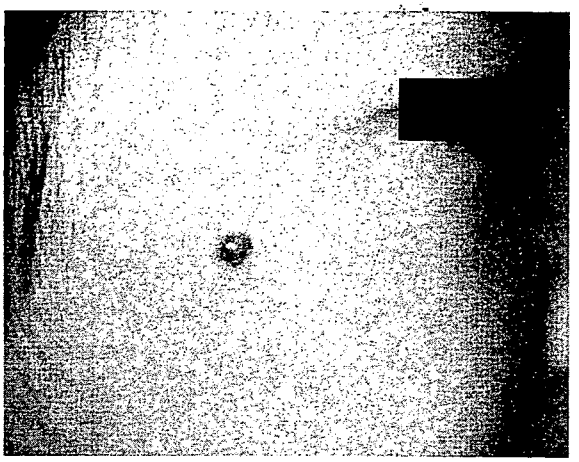

図 19-34　化膿性肉芽腫(5歳，男児，頬部)
出血を繰り返している。

るものとしないものがある。カポジ型血管内皮腫(Kaposiform hemangioendothelioma)と房状血管腫(tufted angioma)は Kasabach-Merritt 症候群に関連した腫瘍で，特に前者は致死的となりうる重篤な疾患である。化膿性肉芽腫(pyogenic granuloma)はしばしば出血の原因となり切除が必要となる(図 19-34)。

図 19-33　先天性血管腫(左下腿)
a：生後 2 週，b：生後 7 か月(退縮途中の外観，中央の皮膚に瘢痕様のひきつれを認める)

9 リンパ管腫

学習のポイント

- リンパ管腫はリンパ管の先天的な発生異常である。
- 頭部(口腔，舌，頬など)，頚部，体幹，四肢などに発生するが，嚢胞状リンパ管腫は頚部，腋窩を好発部位とする。
- 治療は硬化療法(OK-432 など)と外科的切除を組み合わせて行う。

発生・病理

リンパ管腫はしばしば良性腫瘍に分類されるが，その本態は腫瘍性病変ではなくリンパ管(組織)の先天的な発生(形成)異常である。多くは生下時に存在するが，乳幼児期以降に発症することもある。後者の場合はすでに存在していたリンパ管腫にリンパ液の貯留や感染，出血が加わり発症に至ったと理解することができる。

リンパ組織は胎生 6 週頃から発生し，8 週の終わりには 6 個の一次リンパ嚢(primary lymph sac)が存在する(図 19-35)。すなわち，一対の頚部リンパ嚢(jugular lymph sac)，一対の腸骨リンパ嚢(iliac lymph sac)，後腹膜リンパ嚢(retroperitoneal lymph sac)，乳糜槽(cisterna chili)が発生し，その後，頚部リンパ嚢は頭頚部，

上肢に発生したリンパ管と，腸骨リンパ嚢は体幹や下肢のリンパ管と，後腹膜リンパ嚢，乳糜槽は原始腸管のリンパ管と吻合する。またリンパ嚢からはリンパ節が発生する。これらリンパ嚢の発生段階における一部原始リンパ組織の分離やリンパ管との吻合不全によるリンパ流の遮断，停滞などがリンパ管腫の発生原因とも考えられている。

病理組織学的には一層の内皮細胞に囲まれたリンパ液を入れる大小さまざまな腔からなり，間質には結合織，リンパ節，筋線維などを認める。壁の薄い微細なリンパ腔からなる単純性リンパ管腫(lymphangioma simplex)，拡張したリンパ腔からなる海綿状リンパ管腫(cavernous lymphangioma)，数ミリから数センチ径の嚢胞を主成分とする嚢胞状リンパ管腫(cystic lymphangioma, cystic hygroma)に大別され，これらはしばしば混在する。

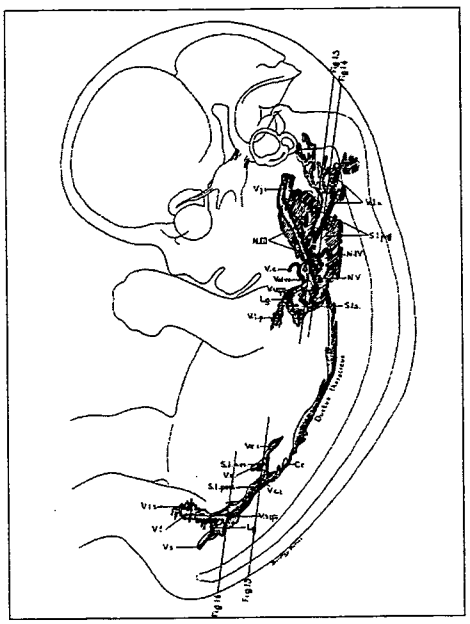

図 19-35 リンパ組織の発生(Sabin，1909)

症状・診断

リンパ管腫は頭部(口腔，舌，頬など)，頚部，体幹，四肢などいずれの部位にも発生するが，嚢胞状リンパ管腫は頚部，腋窩を好発部位とする(図 19-36)。大きさはさまざまで，特に出生前に診断される症例では巨大な外観を呈することが多い(図 19-37)。感染や出血を伴うと腫大し，また経過とともに大きさの変化することがある。後者

図 19-36 頚部から顔面のリンパ管腫

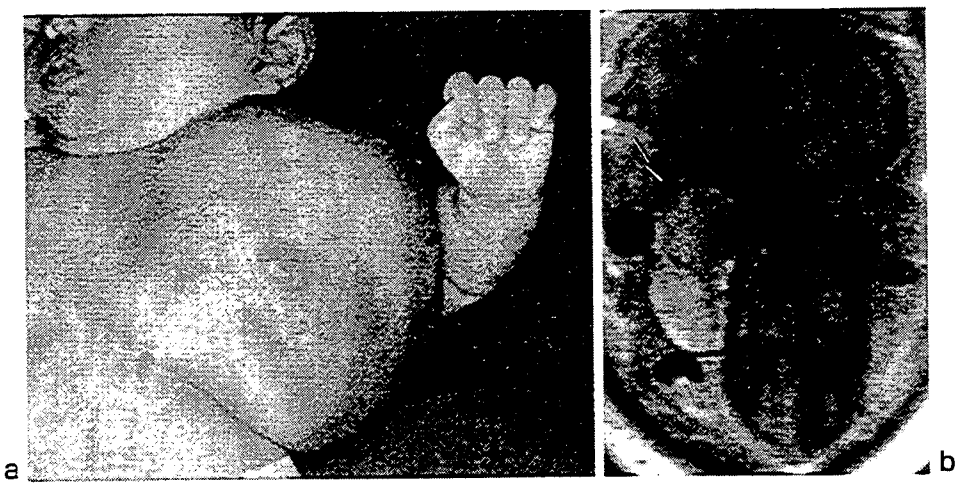

図 19-37 腋窩リンパ管腫の出生前診断

a：生後1か月の外観，b：出生前の MRI(矢印がリンパ管腫)

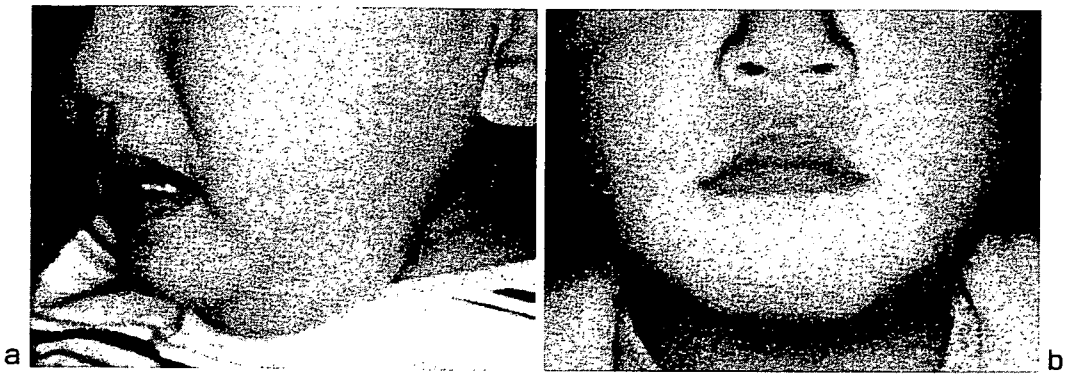

図 19-38　下顎部リンパ管腫(1 歳，男児)の硬化療法
a：OK-432 注入前，b：注入 2 か月後

はリンパ液のうっ滞が原因と考えられ，リンパ管腫の特徴である。

リンパ管腫は弾性軟，表面平滑，境界不鮮明な腫瘤で，嚢胞状リンパ管腫では波動を触知する。皮膚，皮下組織，筋膜，筋などに進展していることが多く，可動性に乏しい。皮膚の色調は出血を伴うと暗紫色を呈する。舌や四肢では粘膜面や皮膚に小水疱を認めたり，出血することもある。無痛性であるが，感染が加わると腫脹，発赤，熱感，疼痛や発熱の原因となる。

舌や前頸部のリンパ管腫は気道や気管を圧迫すると，呼吸障害や嚥下，発語の障害などを引き起こす。後腹膜や腸間膜，大網のリンパ管腫は腸間膜嚢胞，大網嚢胞として腹部腫瘤で発見されたり，腸管の圧迫や軸捻転，腸閉塞の原因となる。腸間膜嚢胞，大網嚢胞は感染を合併すると腹膜刺激症状を伴うので，急性腹症の鑑別診断に含まれる。

診断には超音波検査が有用で，腫瘤内部に薄い隔壁と無エコー域を認めれば理学所見と合わせてリンパ管腫の診断が可能である。進展範囲を正確に把握するためには CT や MRI が必要で，特に詳細な進展範囲の判定には MRI が有用である。

近年，出生前の胎児超音波検査で診断されるリンパ管腫が増加している。特に妊娠早期に診断される頸部の嚢胞状リンパ管腫では Turner 症候群などの染色体異常や胎児水腫，胎児死亡との関連が知られている。Turner 症候群とリンパ管形成異常との関連からリンパ管形成遺伝子が性染色体上に存在すると想定されている。

治療

有症状の場合はもちろん，無症状でも整容を目的に治療が行われる。非手術的治療(硬化療法)は合併症が少ないが，治療効果に乏しいこともある。一方，切除を選択すれば手術痕を残すことになり，合併症の可能性もある。したがって，治療の時期や方法については症例ごとに慎重に判断する。出生前の診断例で呼吸障害の可能性がある場合には周産期集中治療の対象となる。

a) 硬化療法

現在，用いられている薬剤は OK-432(ピシバニール®)とブレオマイシンである。ブレオマイシンは間質性肺炎や肺線維症の発症の危険があるため，使用には注意が必要である。

OK-432 は溶連菌ストレプトコッカス・ピオゲネスをペニシリン処理した菌体成分で，担癌患者の免疫賦活剤として用いられてきた。OK-432 の局注により惹起された炎症により内皮細胞が破壊され，リンパ管腫の縮小をもたらすものと考えられている。

実際には OK-432 を生理的食塩水に溶解し，1 KE(0.1 mg)/10 ml の溶液とし嚢胞の吸引液と置換するか，あるいは局注する。局注後はペニシリンに対する過敏反応に注意する。また 38℃前後の発熱が 3 日間ほどみられ，局所の腫脹，発赤，熱感は 1 週間ほど続く。有効な場合にはその後にリンパ管腫が縮小し，皮膚に壊死や瘢痕を残さない(図 19-38)。3～4 か月間にわたり経過を観察し，必要なら再度局注を行う。治療効果は嚢胞状リン

パ管腫で80～90%以上に有効とされるが，海綿状リンパ管腫では効果に乏しい例も多い。

b）外科的切除

硬化療法で改善がみられない場合は外科的切除を併用する。特に顔面や頚部ではリンパ管腫が神経や血管に接して存在し，慎重な操作を行っても術後に顔面の変形や神経損傷を残す可能性があるため，積極的な切除は避けることが多い。一方，体幹や四肢のリンパ管腫では硬化療法と切除の組み合わせで比較的満足な結果が得られる。しかし，リンパ管腫が広範に進展し残存した場合には，リンパ液の再貯留や再発の原因となる。成長過程にある小児では修復不能な変形や機能障害を残さないように留意すべきであり，手術に際しては形成外科医との協力が欠かせない。

c）出生前診断例の呼吸障害に対する治療

出生前に診断された頚部の巨大なリンパ管腫では，周産期集中治療の対象となる。すなわち，予定帝王切開で児を娩出し，臍帯結紮前の胎盤循環の下で気管内挿管や気管切開を行い気道を確保する。気道が確保できた後は通常の新生児管理を行い，新生児期を過ぎた後にリンパ管腫の治療を開始するのが一般的である。一方，出生前にOK-432の局注を行う胎児治療の試みも報告されている。