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H．知的財産権の出願・登録状況

1．特許取得　　なし
2．実用新案登録　なし
3．その他　　なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）

分担研究報告書

肝血管腫の病理組織及び遺伝子 profile

分担研究者　中澤 温子　国立成育医療研究センター　病理診断部　部長

研究要旨：近年、血管腫と血管奇形を区別することが臨床的に重要であるとの認識が高まっている。乳児血管腫と血管奇形の組織学的鑑別は困難なことが多いが、グルコーストランスポーターの一種である GLUT1 が、乳児血管腫では感度 97%、特異度 100%で陽性となることが報告されている。本研究では、GLUT1, CD31, D2-40 の発現を肝血管腫 6 例について免疫組織化学的に検討した。CD31 は全例で陽性、GLUT1 は 2 例で陽性、D2-40 は全例陰性であった。症例数は少ないが、肝血管腫は、乳児血管腫に分類されるものと血管奇形に分類されるものの２種類があることが判明した。

A．研究目的

肝血管腫（乳児血管内皮腫）は呼吸循環不全や凝固障害などの危急的病態を呈し、速やかな治療効果が得られなければ致死的な疾患である。また、血管腫は発生・分化の過程における血管系の形成異常の側面をもち、肝外病変の存在により、成長、発育を障害する場合もある。低年齢で発見される肝血管腫の頻度は少ないため、危急的病態に対する標準的治療や長期の管理指針は現状では未確立である。加えて治療手技や効果に関するデータは断片的で散在しており、その後の治療に十分に情報を活用できない現状である。本研究では乳幼児期に発生する肝血管腫の内科的、外科的治療のみならず、低年齢児に対する塞栓療法や移植治療など新たな治療戦略を提言するため、病理学的背景を研究することを目的とする

B．研究方法

肝血管腫全国調査（二次）にて、病理診断された症例を抽出し、病理組織学的に検討した。さらに GLUT1, CD31, D2-40 の発現を肝血管腫 6 例についてホルマリン固定パラフィン切片を用いた免疫組織化学染色により検討した。使用した１次抗体は、GLUT1(ウサギポリクローナル抗体, Abcam, x2), CD31(マウスモノクローナル抗体, JC70A, DAKO, x100), D2-40(マウスモノクローナル抗体, D2-40, SIGNET, x100)。CD31, D2-40 は 98℃、40 分（予備加温なし）のウォーターバスによる加熱による抗原賦活化を加えた。免疫組織化学染色はニチレイバイオサイエンス社の自動免疫染色装置（ヒストステイナー48A）を用いて行った。

C．研究結果

病理組織診断は、乳児血管内皮腫 type I が 5 例、 Type II が 1 例であった。CD31 は全例で陽性、GLUT1 は 2 例で陽性、D2-40 は全例陰性であった。
免疫組織化学染色結果からは、乳児血管腫に分類されるものが 2 例、血管奇形に分類されるものが 4 例で、Kaposiform hemangioendothelioma に分類される症例はなかった。

D．考察

乳児血管内皮腫は乳児の肝臓に発生する腫瘍で最も多く、女児に多い。胎生期に発生すると非免疫性胎児水腫を起こし、鬱血性心不全や肝腫大、黄疸などが初発症状となる。

乳児血管内皮腫には、より異型の強い腫瘍細胞からなるものがあり、aggressive な経過をとることが知られている。Dehner、Ishak は乳児血管内皮腫 type II としたが、現在は angiosarcoma に相当すると考えられている。

組織学的には良性であっても、死亡症例１のように生後まもなく呼吸循環不全により死亡する症例がある。年長児あるいは成人で偶然に発見される肝血管腫とは臨床像が全く異なり、腫瘍容積の増大

による呼吸・循環不全や凝固障害など、低年齢児に特異的な病態を呈し、救命困難な症例が少なくない。
近年、肝乳児血管内皮腫と毛細血管の増生を伴う肝血管奇形とをGLUT1の発現で鑑別できるという報告がなされ、自然消退する血管内皮腫と鑑別に有用とされている。乳児血管腫と血管奇形の組織学的鑑別は困難なことが多いが、グルコーストランスポーターの一種であるGLUT1が、乳児血管腫では感度97%、特異度100%で陽性となることが報告されている。GLUT1はKaposiform hemangioendotheliomaやtufted angiomaでは陰性であり、リンパ管内皮マーカーであるD2-40はKaposiform hemangioendotheliomaの結節末梢部に陽性で、tufted angiomaでは陰性である（感度、特異度ともに100%）。このような免疫組織化学的所見から、乳児血管腫に分類されるものが2例、血管奇形に分類されるものが4例で、Kaposiform hemangioendotheliomaに分類される症例はなかった。乳児血管腫と血管奇形の間に、呼吸・循環不全や凝固障害などの臨床所見や、ステロイドやβ-ブロッカーなどの治療に対する反応性があるかどうかは、今後の検討課題である。

E．結論

肝の乳児血管内皮腫は、病理組織学的には、多くはtype Iという良性病変であるが、稀に悪性（type II）がみられ、両者が混在する症例も認められた。また免疫組織化学染色により、乳児血管腫に分類されるものと血管奇形に分類されるものの２種類があることが判明した。

G．研究発表

１．論文発表　　なし
２．学会発表　　なし

H．知的財産権の出願・登録状況

１．特許取得　　なし
２．実用新案登録　なし
３．その他　　なし

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分担研究報告書

新生児および乳児肝血管腫に対する治療の実態把握ならびに
治療ガイドライン作成の研究

難治性肝血管腫に対する肝移植適応

分担研究者　星野　健　　慶應義塾大学　外科学（小児）講師

研究要旨　小児の難治性肝血管腫（本疾患）に対する先進的治療手段である肝臓移植については、詳細な適応がいまだ確立されていない。小児の難治性肝血管腫に対する肝移植の現状を把握する目的で、肝血管腫全国調査（二次調査）から、肝臓移植治療にいたった背景の分析を継続した。新生児期の緊急移植は技術的に克服されれば本疾患に対する究極的な救命手段と成り得ることが期待されるものの、本邦においてはいまだこのような症例の報告はみられなかった。本疾患の慢性期に肝不全徴候を示す症例があり、Low grade malignancy の組織所見を示すものと合わせて亜急性期以降の肝移植適応となっていた。これらを提言に盛り込んだ。

A.　研究目的

肝移植は、小児の難治性肝血管腫（本疾患）に対する究極的な治療手段である。しかしながら本疾患に対する肝移植の詳細な適応ついてはいまだ確立されていない。

昨年度からの本研究では、本疾患に対する治療手段として、interventional radiology，抗がん剤投与、外科的肝切除手術などの治療を選択しえない、あるいはこれらの治療に反応しない症例の現状を調査し、肝移植治療の小児の難治性肝血管腫に対する適応とその意義について後方視的に分析を開始した。今年度は、胎児診断された本疾患症例に対する肝移植の臨床的意義を明らかにする目的で、さらに詳細なケースコントロール研究的検討を行なった。

B.　研究方法

肝血管腫全国調査（二次調査）にて肝臓移植治療がなされた症例を抽出し、病理組織学的検討などの結果をも取り入れて、移植治療にいたった背景を分析した。

C.　研究結果

二次調査により、23 症例のデータが得られた。このうち今年度中にデータの解析が可能であった 19 例の集計が今年度報告されている。この中で、肝臓移植治療にいたった症例の報告は 1 例認められたが、ステロイド治療によって肝血管腫消失後、肝内門脈大循環シャントをともなった肝腫瘤に対する移植症例であった。

集計された 19 例の報告のうち、死亡例は 3 例であり、出生後新生児期早期の死亡である。ステロイド治療は開始されているが、

急激な循環不全、ＤＩＣのコントロールが不能であり失っている。死亡例のうち、外科治療、interventional radiology の介入症例はなかった。

このほか関連疾患を対象とした観察研究として、low grade malignancy を呈する疾患群における最終手段としての肝臓移植症例１例がみられた。二次調査以外のデータであるため、参考症例として扱った。なお病路組織学的検討の詳細は他の分担研究に譲る。

D. 考察

移植治療の対象は、本例に対する内科的（ステロイド、cyclophosphamide, interferon 治療など）、外科的治療（肝動脈 embolization、肝切除）による多角的アプローチが奏功しない症例となる。心不全、凝固異常が亢進し、症状増悪が急激に進行するケースが多く、新生児期に移植がなされているケースはほとんどが緊急移植である。しかし、実際に移植をすべきかどうかの決定、そして移植の至適時期の決定は容易ではない。今回の調査からも新生児期の死亡例にはステロイド治療の導入のみであり、ほかの侵襲的治療の選択すらもできなかったと推測される。昨年度までの調査からは移植治療の意義を検証することはできなかったが、海外の先進的移植施設からの報告では、緊急症例に対する移植、救命例の報告もみられる。

現時点では、本邦における難治性肝血管腫に対する肝移植の適応は、

(1) hemangioendothelioma type 2 のような low grade malignancy の肝血管腫

(2) 多発性肝内門脈肝静脈シャントの形成による肝不全徴候の進行

の２点に限定される。胎児診断された新生児症例の凝固障害など重篤な病態のコントロールのための緊急肝移植に関しては、さらに症例を蓄積して評価する必要がある。

今年度の研究班として策定された「提言」には、これらの文言を盛り込み、肝移植も本疾患に対する選択肢の一つになりうるとする立場を取った。

E. 結論

新生児期の緊急移植は技術的に克服されれば究極の救命手段と成り得ることが期待されるものの、本邦においてはいまだ報告例はみられない。現時点での肝移植適応は亜急性期以降に限定されており、これらを提言に盛り込んだ。

F. 健康危険情報

該当事項なし

G. 研究発表

なし

H. 知的財産権の出願・登録状況

なし

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

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REVIEW ARTICLE

Cellular kinetics of neuroblastoma and the role of surgery

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Abstract Neuroblastoma is known for its peculiar cellular kinetics, which has provoked some controversy regarding surgical treatment. Highly sensitive exploration systems using reverse transcription polymerase chain reaction (RT-PCR) methods have been developed to detect neuroblastoma cells. In our series of 49 patients with advanced neuroblastoma, circulating tumor cells (CTC) were detected by this system in 55.6% of the stage 4 patients who were examined, suggesting that the primary lesion may release tumor cells into the peripheral blood. The Kaplan–Meier survival rate was significantly lower among the patients with CTC or chemotherapy-insensitive bone marrow micrometastasis, compared with those without detectable micrometastasis (33.8 vs. 87.5%, $P < 0.05$). In contrast, a stage 3 patient with MYCN amplification exhibited drastic local relapse without systemic dissemination of the disease. Two patients were positive for CTC without an identifiable primary site. These observations indicate that the local growth of the primary tumor and tumor cell dissemination may be regulated by different molecular mechanisms in neuroblastomas. MYCN amplification seemed to be more closely associated with localized tumor growth but was minimally correlated with CTC positivity. High-risk neuroblastoma may include two separate subgroups characterized by different cellular kinetics: a local risk cohort and a systemic risk cohort. Surgical strategies for neuroblastoma should be determined with taking this cellular kinetics into consideration.

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Keywords Neuroblastoma · Cellular kinetics · Circulating tumor cell · Micrometastasis · Surgery

Introduction

Surgical treatment for neuroblastoma has been controversial. Without a doubt, surgery is a major therapeutic tool for macroscopic lesions. However, not only macroscopic tumors, but also the invisible spreading of tumor cells must be considered in cancer treatment strategies. This consideration is especially important for neuroblastomas, because neuroblastoma has peculiar cellular kinetics. Methods for detecting extremely small amounts of neuroblastoma cells have been developed and applied clinically to some extent, providing some suggestions regarding the cellular kinetics of this disease. On the other hand, the prognostic significance of micrometastasis has not been established for neuroblastomas. In the current review, these problems are described and our own experiences are presented.

Cellular kinetics of neuroblastoma

The unique clinical features are well known in neuroblastoma. Classically, a proportion of infantile patients who show massive metastases to the liver, bone marrow, and skin despite the presence of a small primary tumor has been described and is known as "stage IVS" [1]. The spontaneous regression of both the primary tumor and metastases are commonly observed in this unique population. Subsequently, the role of nerve growth factor and its receptor, trk A, has been clarified in the mechanism of the apoptosis of infantile neuroblastoma [2]. Previously, we reported a series of older cases of neuroblastoma that had no

radiologically identifiable primary tumor despite massive systemic metastases [3]. These clinical observations suggest that the local growth of the primary tumor and the systemic spreading of the tumor cells may be controlled by separate molecular mechanisms in neuroblastomas. The respective factors affecting the growth of primary and metastatic neuroblastomas have not been fully identified at present. How the primary tumor and the metastatic tumors grow independently also remains unknown. From the clinical point of view, studies on the mechanism of this peculiar form of cellular kinetics for neuroblastoma are definitely important in relation to the control of tumor growth and spreading.

Detection of neuroblastoma cells

To trace the cellular kinetics, the development of a highly sensitive method is required to detect neuroblastoma cells. Several methods have been developed to detect tumor cells with a very high sensitivity for some cancers. Immunocytochemical methods can detect tumor cells with a sensitivity of 1/10,000, and clinical applications of these methods have often been reported for patients with leukemia [4–6] as well as neuroblastoma [7, 8]. In the 1980s, molecular biological techniques became widespread. Using reverse transcriptase polymerase chain reaction (RT-PCR) method, a selected sequence of tumor-specific genomic mRNA can be amplified and visualized, enabling the detection of tumor cells amidst more than 10^6 mononuclear cells. More recently, nested PCR or a second PCR to increase the sensitivity even further as well as quantitative PCR have become more common. Several researchers have reported that the quantitative evaluation of the minimal residual disease might provide a higher prognostic value in the selected cancers including neuroblastoma [9–11]. These techniques enable the detection of micrometastases that are totally undetectable using conventional radiological imaging tools and microscopic exploration. Several trials, including our own, have explored the presence of extremely low levels of neuroblastoma cells in the peripheral blood and bone marrow [9, 12–17] (Fig. 1).

On the other hand, the most suitable molecular marker for specific cancers has not been established for many malignancies. Some markers provide a higher sensitivity, but a lower specificity. Tyrosine hydroxylase, PGP9.5 [18, 19], and, more recently, GD2 synthetase [20], GAGE [21], and cyclin D1 [22] have been named as specific markers of neuroblastoma cells. More than 95% of neuroblastomas exhibit a catecholamine biosynthesis pathway in their tumor cells [23]. Tyrosine hydroxylase is the first and rate-limiting enzyme of this pathway, and specifically expressed in most neuroblastoma cells. Thus, tyrosine hydroxylase

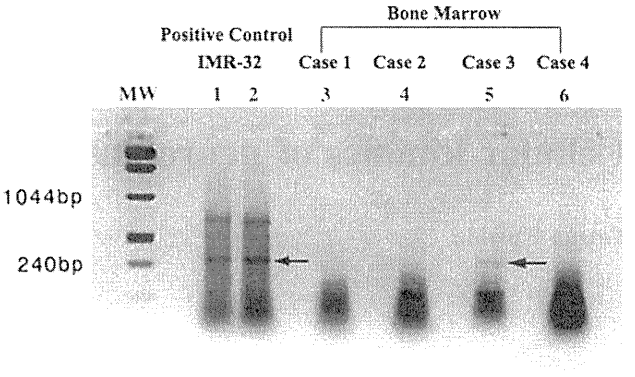

Fig. 1 Exploration of bone marrow micrometastasis of neuroblastoma using a single PCR method. *Lanes 1* and *2* IMR-32 cell line as the positive control. *Lanes 3–6* bone marrow samples harvested from four neuroblastoma patients. *Case 3* (*Lane 5*) showed positive signal for neuroblastoma at 256 bp, as observed in the positive control

mRNA is most commonly used as a molecular marker for neuroblastoma cells. Practically, several types of tyrosine hydroxylase mRNA synthesized using alternate splicing in exons 1 and 2 have been identified [24–26]. Therefore, the primers are usually designed to encode a common sequence region so as to detect all types of tyrosine hydroxylase mRNA [27].

The appropriate sensitivity of the PCR exploration is another problem that remains unsolved. The expression of genomic mRNA by contaminated leucocytes in a very small amount has been described as ectopic RNA. Two-step PCR methods possibly detect these non-specifically expressed mRNA [28]. Future clinical studies may be directed to standardize the methodology employed to detect micrometastatic neuroblastoma. Therefore, at present, all the staging and risk grouping systems are based on light microscopic observation.

Circulating tumor cells

In our own series of 49 patients with advanced neuroblastoma, who were treated between 1991 and 2007, circulating tumor cells (CTC) in the peripheral blood were detected in 55.6% of the stage 4 patients using our previously described single RT-PCR method [29]. The above two patients who exhibited massive metastases without an identifiable primary site also presented CTC positivity regardless of MYCN copy numbers. All the deaths in this cohort of patients with CTC were related to the systemic dissemination of the disease. CTC positivity was not detected in any of the stage 3 patients at this sensitivity level. The detection of CTC was not associated with MYCN amplification. The positive rate was 44.4% among the patients with amplified MYCN and 46.2% among the

patients with a single copy of MYCN [29]. Clinically, 75% of the patients who developed relapse with disseminated metastasis, had a single copy of the MYCN oncogene, whereas all the patients who developed local tumor relapse, showed amplification of MYCN (although the number of patients in this group was not large) [3].

These clinical observations suggest the following hypothetic model explaining the cellular kinetics in neuroblastomas. Tumor cells may grow at the primary site and, simultaneously, translocate into the peripheral blood as CTC to form distant metastases, which may be regulated by molecular mechanisms other than those controlling the local tumor growth (Fig. 2). Potentially, these primary and metastatic lesions may both become sources of CTC. Although the amplification of the MYCN oncogene is closely associated with localized tumor growth, it may be minimally correlated with the systemic dissemination of the disease.

In addition, these observations highlighted the existence of two clinical subgroups exhibiting different cellular kinetics in advanced neuroblastoma patients: a systemic risk cohort with CTC positivity, and a local risk cohort characterized by MYCN amplification but without micrometastasis. These two cohorts may correspond to the two categories in the INRG high-risk group [30].

Prognostic significance of micrometastasis

Although the prognostic significance of micrometastasis or CTC in the peripheral blood is better established for some of the hematological cancers, it remains controversial in neuroblastoma [9, 12–15]. We reported previously that the Kaplan–Meier survival rate was 42.0% in patients with CTC positivity in our series, and was definitely lower than that of 90.0% of the patients with no detectable CTC [29]. In our series, micrometastasis to the bone marrow was detected in 72.2% of the stage 4 patients who were examined. The positive rate was 85.7% in the patients with CTC positivity and 50% in the patients without detectable tumor cells in the peripheral blood. The temporary appearance of bone marrow micrometastasis did not affect the clinical outcome in our series. However, the persistent bone marrow micrometastasis after chemotherapy, which was detected in half of the patients, seemed to be associated with a poor prognosis. Combining these results, the Kaplan–Meier analysis showed a statistically significant difference in the survival rate between patients with CTC positivity and/or persistent bone marrow micrometastasis and those without detectable micrometastasis (33.8 vs. 87.5%; $P < 0.05$). Thus, our observations support a hypothesis that the presence of micrometastasis can be regarded as an independent clinical risk factor other than MYCN amplification, and has strong clinical implication on the determination of treatment strategy in advanced neuroblastoma. Similar observation regarding the bone marrow micrometastasis was also reported from Japan [31]. In addition, since these micrometastases are often chemotherapy resistant, they may include a cancer stem cell-like population of neuroblastoma cells, such as side population cells or tumor-initiating cells. More recently, Hansford et al. [32] succeeded in identifying a highly tumorigenic cell population in the bone marrow of neuroblastoma patients. Future study may be directed to control the proliferation of these cell populations.

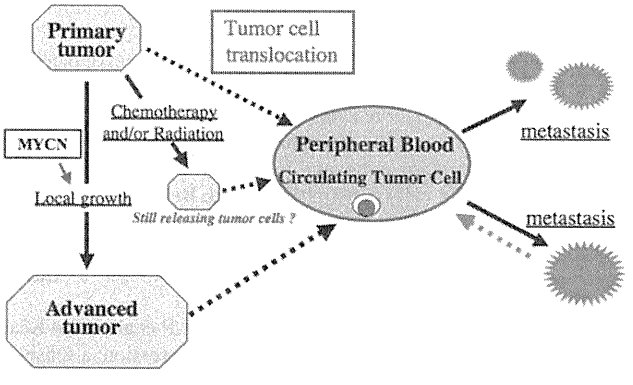

Fig. 2 Hypothetic model for cellular kinetics of neuroblastoma

Optimal local treatment

In recent concepts for neuroblastoma surgery, risk assessment has been emphasized in the design of surgical strategies. Different strategies should be applied according to the risk assessment. Image-defined risk factor (IDRF) is a recently proposed concept used to evaluate image diagnostic findings in a standard manner in relation to the risk groupings of neuroblastoma [33]. In infants with low or intermediate risks who exhibit IDRFs, surgical extirpation may be abandoned. The risk benefit balance of surgical treatment and presumably a benign tumor biology determine the surgical strategy. An analysis of molecular markers provides important information regarding the biological features of tumors, enabling surgical risks to be avoided.

Among the high-risk patients, aggressive surgery would benefit patients in the local risk cohort the most. In contrast, for those in the systemic risk cohort, the clinical impact of intensive surgical treatment remains unestablished [34]. Several studies, including ours, have demonstrated the clinical significance of intensive local treatment for neuroblastoma patients with stage 4 disease, whereas other studies have not [35–37]. We previously observed that no local relapse occurred after completing total resection of the primary tumor, systemic lymph node

dissection, and intraoperative radiation (IOR) [35]. Nevertheless, all the patients with macroscopic residual tumor died within 1 1/2 year after surgery because of systemic metastasis in this series. These observations suggest that surgical eradication may be essential for long-term survival in all patients with high-risk neuroblastomas. The primary tumor might still act as a source of neuroblastoma cells which are released into the peripheral blood, even after chemotherapy and IOR, possibly resulting in systemic relapse. Hypothetically, local control may also play an important role in controlling the systemic dissemination of the disease. If so, reducing the surgical intensity could be considered dangerous also in patients with metastasis. Further studies would be still required to determine if surgical intensity could be reduced even for the cases of the systemic risk cohort.

On the other hand, an interesting clinical trial is now in progress in Japan. This novel trial is characterized by non-stop chemotherapy until mega-therapy with stem cell transplantation, combined with delayed local therapy, including surgery, until the end of the treatment course [38]. The most beneficial aspect of this new protocol is the avoidance of delays in chemotherapy because of surgical complications.

Consideration of quality of life during the distant post-therapeutic period

Another aspect that should be considered when deciding on the surgical strategy is the securement of a satisfying post-therapeutic quality of life. A high incidence of morbidity has been associated with intensive local treatment [39, 40]. IOR can be used to control the primary site completely; however, the morbidity rate after intensive surgery with IOR was as high as 33.3% in our series. Renal vascular problems were seen in 15.2% of the patients, representing the most common complication after IOR [41]. Thus, modern surgical guidelines for advanced neuroblastoma recommend less harmful surgery and lymph node sampling instead of systemic dissection, and direct to avoid resection of surrounding organs.

Conclusions

In summary, both local and systemic risk must be considered when deciding on a surgical strategy. Some of the clinical observations presented above suggest that local control and systemic control therapies for neuroblastoma may interfere with each other. Therefore, a suitable balance between local and systemic therapy is extremely important for the treatment of neuroblastoma. The suitability of surgical therapy for neuroblastoma should be discussed also based on the observations of the cellular kinetics. Molecular biological tools may help pediatric surgeons to make appropriate decisions by providing a more detailed risk assessment in relation to the cellular kinetics.

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Critical infantile hepatic hemangioma: results of a nationwide survey by the Japanese Infantile Hepatic Hemangioma Study Group

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Key words:
Infantile hepatic hemangioma;
Hemangioendothelioma;
Liver transplantation;
β-blocker

Abstract

Background: The current survey aimed to describe the clinical features of critical infantile hepatic hemangioma (IHH) and the implications of recent treatments.

Materials and Methods: A nationwide survey of critical IHH patients treated between 2005 and 2010 was performed in all 117 registered pediatric surgical hospitals in Japan. As a result, 19 patients were identified and reviewed using a statistical analysis.

Results: Abdominal distention (47.4%), high-output cardiac failure (47.4%), coagulopathy (42.1%), and respiratory distress (31.6%) were the major symptoms. Three patients died (1 of coagulopathy, 1 of cardiac failure, and 1 of both). An accompanying portovenous shunt was also highlighted. Infantile hepatic hemangioma was totally insensitive to steroid treatment in 3 (23.1%) of the 13 patients, and 9 (47.4%) of the 19 patients required other treatments. Surgical resection and β-blocker improved the hematologic data, whereas hepatic arterial ligation and embolization seemed to produce a limited effect. Among the dead patients, several hematologic parameters were significantly worse: the thrombocyte count (pretherapeutic: 73 000 vs 300 000/mm^3, dead vs survivor, respectively [$P < .03$]; posttherapeutic: 66 000 vs 388 700/mm^3 [$P < .003$]) and the prothrombin time (posttherapeutic, 35.0 vs 12.1 seconds [$P < .0001$], dead vs survivor, respectively).

Conclusion: For critical IHH cases with steroid-insensitive hematologic disorders, alternative treatments including β-blocker therapy, surgery, and liver transplantation should be considered.

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A certain proportion of hepatic hemangiomas seen in neonates and infants has been known to cause critical complications such as high-output cardiac failure and coagulopathy and are considered potentially fatal. This subtype of infantile hepatic hemangioma (IHH) is rare but may be regarded as a distinct clinical entity because of its unique and critical features. Nevertheless, the precise clinical features of IHH including the predictive risk factors are not well known. Steroid treatment is most commonly used for hemangiomas; however, the efficacy for the IHH patients has not been established. On the other hand, novel therapeutic options such as β-blocker therapy and liver transplantation have been applied to the critical cases. The current nationwide survey aimed to describe the clinical features and the implications of treatment options for critical IHH.

1. Materials and methods

A primary survey on IHH was sent to all 117 pediatric surgical institutions nationwide that are registered with the Japanese Society of Pediatric Surgeons after receiving the permission of the academic board of the association. Based on the results of the primary survey, a more detailed secondary survey was mailed to the 38 institutions that possibly treated the IHH patients during the last 5 years. Nineteen IHH infants (8 males and 11 females) who required treatments under the age of 1 year, between January 2005 and December 2010, were identified in 11 institutions by the secondary survey and were involved in the current study. The patients were treated respectively according to the local protocol of each hospital for IHH. Their relevant clinical courses, biochemical and hematologic data, pathologic images, and radiologic images were collected to construct a database and then analyzed using a statistical analysis (t test) under the permission of the institutional review board of the National Center for Child Health and Development (No. 2010-440).

The age at the time of diagnosis ranged from 0 to 9 months (median, 1 month), the birth weight ranged from 966 to 3340 g (median, 2757g), and the gestational period ranged from 27 weeks and 3 days to 41 weeks and 3 days (median, 38 weeks and 3 days).

2. Results

2.1. Clinical symptoms

Abdominal distention (47.4%), high-output cardiac failure (47.4%), coagulopathy (42.1%), and respiratory distress (31.6%) were the major symptoms. Liver dysfunction (15.9%), renal failure (10.6%), hepatosplenomegaly (5.3%), hypertrophic cardiomypathy (5.3%), hypothyroidism (5.3%), and failure to thrive (5.3%) were also observed. Hypergalactosemia with hyperammonemia was observed in 2 patients, and congenital cystic adenomatoid malformation of the lung and Beckwith-Wiedemann syndrome was observed in 1 patient each. Three patients in the series died during the neonatal period: 1 died of coagulopathy, 1 died of cardiac failure, and 1 died of both coagulopathy and cardiac failure. The lesions were located in the 4 segments of the liver with a similar incidence. Four patients (21.1%) had extrahepatic hemangiomas, all of which were skin lesions.

Eleven patients had a solitary lesion, whereas 8 patients had multifocal lesions (2-10 lesions) in the liver. The size of the lesion ranged from 25 to 100 mm in the maximum diameter. Of the 3 patients who died, 2 had a huge solitary lesion (>80 mm in the maximum diameter) and another had multifocal lesions; however, no significant correlation was observed between the tumor size and prognosis in the present series. Histopathologic data were available for 7 patients; a hemangioendothelioma was observed in 3 patients (type 1 in 1, subtype unknown in 2), a cavernous hemangioma was observed in 3, and a large portohepatic venous shunt was observed in 1 after the regression of IHH. Of the 3 patients with hemangioendothelioma, 2 died, whereas all the patients with cavernous hemangioma survived.

2.2. Treatments

Prednisolone (0.5-10 mg/kg) was administered to 13 patients for a period of 3 days to 9 months; 3 of these patients experienced complete remission of the lesion, and 7 showed a partial regression. However, IHH was totally insensitive to steroid treatment in 3 patients (23.1%), and 9 (47.4%) of the 19 patients required treatment other than steroids. α-Interferon and vincristine were each administered to 1 patient, but only minimal responses were observed. In contrast, a patient who was given 2.5 mg/kg of propranolol, a β-blocker, exhibited a rapid improvement of hematologic data within a week after administered. Two patients underwent radiation therapy (2-3.5 Gy) at the age of 0 to 1 month, which also induced the regression of IHH. Hepatic arterial embolization was performed in 1 steroid-resistant patient at the age of 0 month; however, the hepatic lesion and the hematologic data did not improve significantly, and the patient died. Four patients underwent surgical intervention: a hepatic resection was performed in 3 patients, and hepatic arterial ligation was performed in 1 patient. Surgical resection sufficiently improved the thrombocyte count (206,300 ± 258,800 to 400,700 ± 97,200/mm^3) and the prothrombin time (PT) (28.5 ± 18.9 to 13.0 ± 1.6 seconds), whereas hepatic arterial ligation had a limited effect.

A patient with multifocal lesions developed hepatic vascular malformation with progressive liver dysfunction after the regression of IHH as a result of steroid therapy and subsequently underwent a liver transplantation at the age of 1 year and 10 months.

Three dead patients were all treated with steroid initially without sufficient response, then one of them underwent embolization, and another received vincristin, which all failed to control the critical conditions.

2.3. Risk assessment

Among the pathologic, cardiac ultrasonographic, biochemical, and hematologic parameters that were assessed in relation to the prognosis, no significant difference was observed in the biochemical parameters of liver function and cardiac ultrasonographic parameters between the patients who died and those who survived. Only the thrombocyte count (73 300 ± 52 900 vs 300 000 ± 195 600/mm^3 before treatment [$P < .03$], 66 300 ± 20 200 vs 388 700 ± 118 300/mm^3 after treatment [$P < .003$]) (Fig. 1) and the posttherapeutic PT (35.0 ± 14.7 vs 12.1 ± 1.4 seconds [$P < .0001$]) (Fig. 2) exhibited significant deterioration among the patients who died. Furthermore, these hematologic parameters improved after treatment in the survivors, whereas they deteriorated even after treatment in the patients who died.

3. Discussion

Hemangioma is a benign vascular endothelial neoplasm and one of the most common benign tumors seen in the liver during childhood [1]. However, the description of its natural course is still confusing in the literatures. Although most hepatic lesions are asymptomatic, a very small proportion leads to the development of critical pathophysiologies such as high-output cardiac failure and microangiopathic consumptive coagulopathy because of the highly increased vascular bed within the tumor. Consequently, patients may experience a fatal clinical course, often during the first year of life. Recently, Christison-Lagay et al [2] reviewed the previous reports on the critical

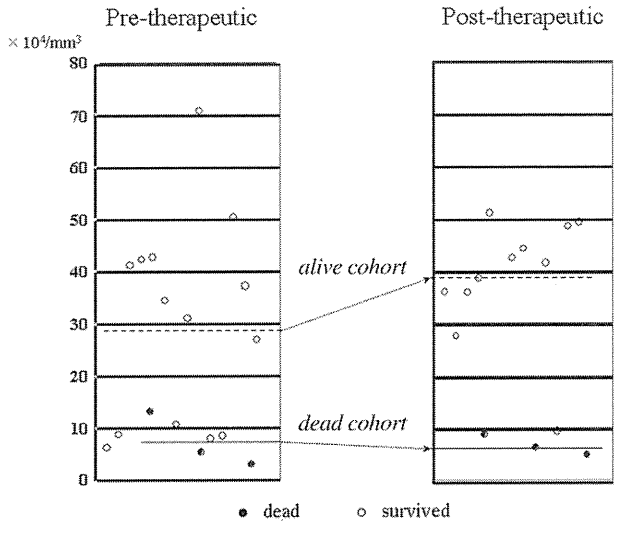

Fig. 1 Pre- and posttherapeutic platelet counts. Platelet count was not improved after treatment in the patients who died. Both pre- and posttherapeutic platelet counts were significantly deteriorated in the patients who died. Open circles indicate patients who survived; closed circles, patients who died.

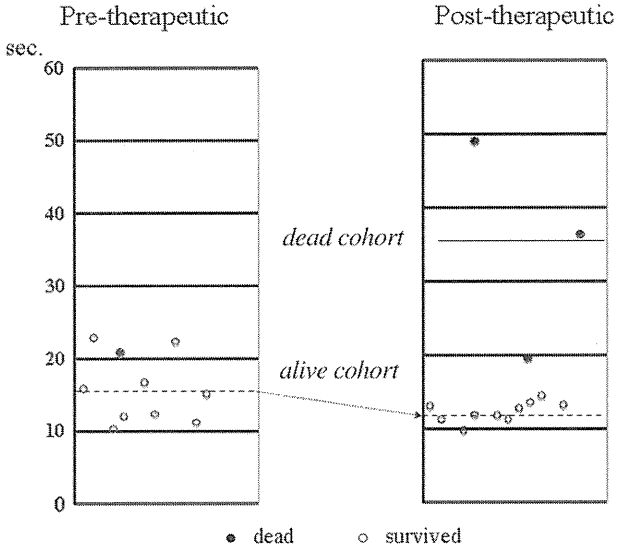

Fig. 2 Pre- and posttherapeutic PT. Posttherapeutic PT was significantly deteriorated in the patients who died. Open circles indicate patients who survived; closed circles, patients who died.

hepatic hemangiomas and proposed that critical IHH be regarded as a distinct clinical entity. They also pointed out that diffuse lesions are more closely associated with critical complications. Nevertheless, because of the rarity of the patients, the precise clinical features and the treatment strategy for critical IHH have not yet established. To describe the precise clinical features in relation to the risk assessment and to study the efficacy of novel treatment options for fatal symptoms, the current survey aimed to accumulate the latest clinical information on critical IHH patients nationwide by surveying all registered pediatric surgical institutions in Japan.

Nineteen infantile patients who underwent treatment for IHH during the last 5 years were identified throughout Japan. The current series is not large despite a nationwide search because only the recent patients were targeted to assess the modern therapies. Although half of the patients required alternative therapeutic options other than steroids, 16 of the 19 patients survived. Critical circulatory failure and respiratory distress were again highlighted as the major symptoms in the current series. In addition, liver dysfunction and renal failure were also observed as potentially coexisting pathophysiologies. Hypothyroidism, that was often described in the previous reports, was observed in only 1 patient in the present series, suggesting that potential hypothyroidism in IHH might not be assessed completely. Of 4 syndromic patients, 2 were considered to have hypergalactosemia arising from a portovenous shunt. In 1 case, a large portovenous shunt developed after the regression of the hepatic lesions, and a liver transplantation was subsequently required at the older age. Future study is necessary to clarify whether a portovenous shunt may congenitally coexist with vascular neoplasms or is acquired by the transformation of a hemangioma.

In the present survey, not only the patients with diffuse lesions but also those with solitary lesions died of the critical pathophysiologies unlike the previous observations have suggested. Regarding the histopathology, hemangioendothelioma, especially type 2 disease, is reportedly associated with rapid growth and critical symptoms [3]. The current observation suggests that any subtypes of hemangioendothelioma may be potentially associated with high risk. Among the clinical parameters, a decreased platelet count and a prolonged PT are significantly associated with a fatal outcome. The unresponsiveness of hematologic data to the initial therapy may be strongly predictive for high risk than diffuse radiologic findings. Because all of the dead patients died within 30 days after birth, the rapid improvement of critical condition in response to the treatment is thought to be necessary for survival.

Regarding treatment, steroid therapy has been considered the gold standard for hemangioma; however, almost a quarter of the patients did not show any response to steroids in the present series. Other than steroid therapy, α-interferon therapy, chemotherapeutic agents such as vincristin [4,5], actinomycin D, cyclophosphamide [6], and more recently, propranolol (a β-blocker) [7,8] have also been reported to be effective for the medical treatment of hemangiomas, including IHH. In the current series, interferon, vincristine, and propranolol were administered to steroid-resistant patients, but only propranolol rapidly improved the hematologic disorders.

Arterial embolization has also been reported to be effective for the treatment of steroid-resistant IHH [9]; however, a steroid-resistant case that underwent embolization in the current series did not exhibit an improvement in coagulopathy. Interestingly, a patient who underwent a laparotomy and hepatic arterial ligation also did not show a lasting effect. These observations suggest that hepatic arterial intervention may not be capable of strongly controlling the critical coagulopathy and tumor growth. In contrast, a marked improvement in the hematologic data was obtained after the surgical resection of IHH. This may reflect the less critical condition of the patients who were supposed to tolerate a laparotomy. Liver transplantation is one of the latest therapeutic options for IHH. According to the United Network for Organ Sharing (UNOS) report [10] surveying patients of all ages, 110 patients with an average age of 36 years underwent 126 liver transplantations for hepatic hemangioendothelioma between 1987 and 2005, and the 5-year survival rate was 64%. Markiewicz-Kijewska et al [11] reported 4 infantile cases of urgent liver transplantation for hemodynamic failure. Thus, transplantation may be indicated also for urgent cases with hemodynamic failure.

Based on the above observations, an algorithm of treatment strategy for IHH may be summarized as shown in Fig. 3. For critical IHH cases showing steroid-insensitive thrombocytopenia and PT prolongation, novel therapeutic options including β-blocker therapy, surgery, and liver

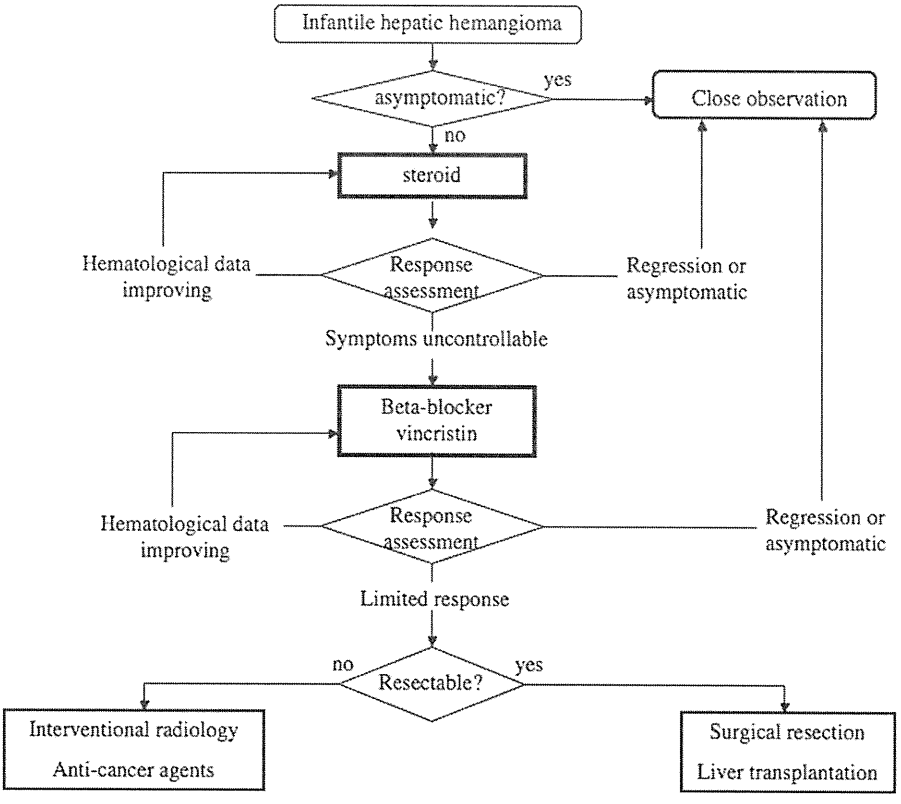

Fig. 3 A proposed algorithm of treatment for IHH.

transplantation should be considered urgently as the alterative treatment.

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