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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Pediatrics / Pediatri

Etiological Evaluation of Patients with Hepatomegaly, Splenomegaly, and Hepatosplenomegaly Referred to a Pediatric Metabolism Unit

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ABSTRACT

Objective: Hepatomegaly, splenomegaly, and hepatosplenomegaly in children can be due to various disorders, and also inborn errors of metabolism (IEM). Some IEM's have specific treatments which should be started before irreversible complications occur. The aim of this study is to evaluate the etiological causes of visceromegaly in pediatric patients, and assess the clinical findings of patients having an IEM.

Materials, and Methods: In this study, medical records of 93 patients who were referred to a Pediatric Metabolism Unit in a tertiary care hospital with the suspicion of IEM-related hepatomegaly, splenomegaly, or hepatosplenomegaly were reviewed retrospectively.

Results: 45 patients had hepatomegaly, 18 had splenomegaly, and 30 had hepatosplenomegaly. A total of 52 patients were diagnosed as having an IEM. In hepatomegaly group; diagnoses were glycogen storage disease (GSD)(51,1%), cholesteryl-ester storage disease (4,4%), galactosialidosis (4,4%), mucopolysaccharidosis (4,4%), multiple-acyl-CoA dehydrogenase deficiency (2,2%), hereditary fructose intolerance (2,2%), and GM1 gangliosidosis (2,2%). In splenomegaly group; diagnoses were Gaucher disease (22,2%), Niemann-Pick disease type C (NPC)(16,6%), and Niemann-Pick disease type A/B (NPAB)(11,1%). In hepatosplenomegaly group; diagnoses were Gaucher disease (13,3%), NPC (6,6%), NPAB (6,6%), GSD (3,3%), mucopolysaccharidosis (3,3%), and infantile sialic acid storage disease (3,3%). 32 patients were lost to follow-up. The eventual diagnoses of 9 patients were not IEM.

Conclusion: IEMs present from the prenatal period to adulthood. Awareness of clinicians, and diagnostic algorithms can prevent delayed diagnosis, and enable early treatment for treatable IEMs or provide genetic counseling for the patient's family.

Keywords: hepatomegaly, splenomegaly, hepatosplenomegaly, inborn errors of metabolism

Çocuk Metabolizma Ünitesine Hepatomegali, Splenomegali ve Hepatosplenomegali Nedeniyle Sevk Edilen Pediatrik Hastaların Etiyolojik Değerlendirmesi

ÖZET

Amaç: Çocuklarda hepatomegali, splenomegali ve hepatosplenomegali; pek çok hastalığa ve ayrıca kalıtsal metabolik hastalıklara (KMH) bağlı olarak görülebilir. Bazı KMH'ların spesifik tedavileri olup geri dönüşsüz komplikasyonlar gelişmeden başlanması gereklidir. Bu çalışmanın amacı pediatrik hastalarda viseromegali etiyolojisinin değerlendirilmesi ve KMH tanısı alan hastaların klinik bulgularının irdelenmesidir.

Gereç ve Yöntem: Bu çalışmada, üçüncü basamak bir hastanede KMH'a bağlı hepatomegali, splenomegali ve hepatosplenomegali olduğundan şüphelenilerek Çocuk Metabolizma Bölümü'ne sevk edilen 93 hastanın tıbbi kayıtları geriye dönük olarak incelenmiştir.

Bulgular: 45 hastada hepatomegali, 18 hastada splenomegali ve 30 hastada hepatosplenomegali saptandı. Toplam 52 hasta KMH tanısı aldı. Hepatomegali grubunda tanılar glikojen depo hastalığı (GSD)(51,1%), kolesteril ester depo hastalığı (4,4%), galaktosiyalidozis (4,4%), mukopolisakkaridozis (4,4%), multipl-açil-KoA dehidrogenaz eksikliği (2,2%), herediter fruktoz intoleransı (2,2%) ve GM1 gangliyosidozis (2,2%) idi. Splenomegali grubunda tanılar Gaucher hastalığı (22,2%), Niemann-Pick hastalığı tip C (NPC)(16,6%) ve Niemann-Pick hastalığı tip A/B (NPAB)(11,1%) idi. Hepatosplenomegali grubunda tanılar Gaucher hastalığı (13,3%), NPC (6,6%), NPAB (6,6%), GSD (3,3%), mukopolisakkaridozis (3,3%), and infantil siyalik asit depo hastalığı (3,3%) idi. 32 hasta klinikte takibe devam etmedi. 9 hastaya KMH dışında tanılar konuldu.

Sonuç: KMH'lar prenatal dönemden erişkin yaşlara kadar bulgu verebilmektedir. Klinisyenlerin farkındalığının arttırılması ve tanısal algoritmalar, tanıda gecikmeyi engelleyebilir ve tedavisi olan KMH'lar için erken tedaviyi ve hastaların ailelerine genetik danışma verilebilmesini sağlayabilir.

Anahtar Kelimeler: Hepatomegali, splenomegali, hepatosplenomegali, kalıtsal metabolik hastalıklar

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The etiology of hepatomegaly (HM), splenomegaly (SM), or hepatosplenomegaly (HSM) in a pediatric patient is associated with infections, genetic liver diseases, hematological diseases, or malignancies, autoimmune disorders, passive congestion as well as inborn errors of metabolism (IEM) (1,2). Visceromegaly is an important finding in pediatric patients referred to investigate underlying etiology. Extensive diagnostic is usually needed in such patients. A national etiological study regarding splenomegaly was reported which was conducted in both pediatric, and adult patients, and none of the patients were diagnosed as having an IEM. The most frequent diagnoses were hematological conditions in this study (1). Clinicians usually investigate frequent non-IEM disorders in the beginning, and when the etiological workup does not bring diagnosis when an IEM is suspected. Timely diagnosis of an IEM enables genetic counseling providing future healthy pregnancies for the patient's family and specific therapeutic interventions before the development of irreversible complications for treatable IEM's. The purpose of this study is to uncover the etiological causes of visceromegaly in pediatric patients who were suspected to have an IEM.

MATERIALS and METHODS

Sample

Medical records of pediatric patients who were admitted to Adana City Research, and Training Hospital, Pediatric Metabolism Department between December 2018, and December 2020, and had hepatomegaly, splenomegaly, or hepatosplenomegaly were reviewed retrospectively. Accordingly, the sample of the study included 93 patients. Hepatomegaly, splenomegaly, or hepatosplenomegaly were defined as enlargement of the liver, and/or spleen according to patient's age either detected by physical examination of two separate clinicians or by ultrasonography (3). Sociodemographic data (gender, age, nationality, parental consanguinity, similar family history, clinicians that referred the patients, current status of patients), growth parameters (weight, and height), clinical, laboratory, and imaging findings, and eventual diagnoses of patients were noted. Eventual diagnoses of patients were confirmed by enzyme analyses, and/or molecular analyses.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 23.0, Chicago, IC, USA) program was used for statistical analysis. Results were presented as mean, and standard deviation for numerical variables, and frequency, and percentage for categorical data. The normality of the quantitative data was evaluated by using the Kolmogorov-Smirnov test. To assess non-parametric data the Mann Whitney U test was used to compare numerical variables between two independent groups, and the Kruskal-Wallis test was used in comparing more than two independent groups. p values <0.05 were accepted as statistically significant.

RESULTS

There were 93 patients with visceromegaly; of which 45 had hepatomegaly, 18 had splenomegaly, and 30 had hepatosplenomegaly. 36 were female, 57 were male. 43% of the patients were Syrian refugees. 78,5% of patients had parental consanguinity, and 34,4% had a positive family history. Patients' mean current age was 56,9±49,8 months. 10 patients died during follow-up. 32 patients were lost to follow-up during the COVID-19 pandemic. Patients were referred due to suspicion of an IEM by pediatricians (47,3%), pediatric gastroenterologists (33,3%), pediatric hematologists (16,1%), pediatric neurologists (2,2%) or pediatric endocrinologists (1,1%). None of the patients had lymphadenopathy. None of the patients had splenectomy.

Patients were reviewed according to groups. In the hepatomegaly group; eventual diagnoses were glycogen storage disease (GSD) in 23 patients (51,1%), cholesteryl-ester storage disease (CESD) in 2 patients (4,4%), galactosialidosis in 2 patients (4,4%), mucopolysaccharidosis in 2 patients (4,4%), multiple-acyl-CoA dehydrogenase deficiency (MADD) in one patient (2,2%), hereditary fructose intolerance in one patient (2,2%), and GM1 gangliosidosis in one patient (2,2%) (Figure 1). One patient with hepatomegaly was eventually diagnosed as having alpha-1 antitrypsin deficiency. 12 (26,6%) patients without a specific diagnosis were lost to follow-up. Patients in the hepatomegaly group had the highest rate of parental consanguinity, and positive family history (Table 1). 8,9% of patients had leukopenia and were diagnosed with GSD type 1a. 8,9% had anemia, and 6,7% had thrombocytopenia (Table 2).

Specific diagnoses of the patients with isolated splenomegaly were Gaucher disease in 4 patients (22,2%), Niemann-Pick disease type C (NPC) in 3 patients (16,6%), and Niemann-Pick disease type A/B (NPAB) in 2 patients (11,1%) (Figure 1). One patient with splenomegaly was eventually diagnosed with immune deficiency. 8 (44,4%) patients had no specific diagnoses and were lost to follow-up. In the splenomegaly group; 55,6% had thrombocytopenia, 55,6% had anemia, and 16,7% had leukopenia (Table 2).

Table 1. Sociodemographic data, growth parameters, and multisystemic involvement of patients according to type of visceromegaly

	Total N (%)	IEM N (%)	Parental consanguinity %*	(+) family history %*	Weight SDS	Height SDS	Liver steatosis %*	Neonatal cholestasis %*	Neurological deficit %*	Eye involv. %*	Cardiac involv. %*
HM	45 (48,3)	32 (71,1)	84,4	44,4	-1,08±1,59	-1,88±1,48	53,3	6,7	11,1	2,2	4,4
SM	18 (19,3)	9 (50)	66,7	27,8	-0,77±1,45	-0,89±1,09	0	16,7	27,8	0	5,6
HSM	30 (32,2)	11 (36,6)	76,7	23,3	-1,42±1,94	-1,91±1,88	6,7	16,7	33,3	3,3	7

HM: Hepatomegaly, HSM: Hepatosplenomegaly, IEM: Inborn errors of metabolism, Involv.: involvement, N: Number, SDS: Standard deviation score, SM: Splenomegaly, (+): Positive
*: Percentage within the subgroup

Table 2. Laboratory evaluation of patients according to type of visceromegaly

	Leukopenia %*	Anemia %*	Thrombocytopenia %*	Elevated liver enzyme %*	Low HDL levels %*	Hyperlipidemia ⫛ %*	Low blood glucose %*	Hyperuricemia %*	Elevated INR %*	Elevated AFP %*
Hepatomegaly	8,9	8,9	6,7	68,9	0	46,7	26,7	13,3	11,1	13,3
Splenomegaly	16,7	55,6	55,6	44,4	38,9	0	0	5,6	5,6	11,1
Hepatosplenomegaly	30	63,3	70	63,3	16,7	16,7	0	0	20	26,7

AFP: Alpha-fetoprotein, INR: International normalized ratio
*: Percentage within the subgroup
⫛: Hypercholesterolemia, and/or hypertriglyceridemia

Eventual diagnoses of the patients with hepatosplenomegaly were Gaucher disease in 4 patients (13,3%), NPC in 2 patients (6,6%), NPAB in 2 patients (6,6%), GSD in one patient (3,3%), mucopolysaccharidosis (MPS) in 1 patient (3,3%), and infantile sialic acid storage disease (ISSD) in one patient (3,3%) (Figure 1). Three patients with hepatosplenomegaly were diagnosed as having familial hemophagocytic lymphohistiocytosis (HLH). Two patients with hepatosplenomegaly were diagnosed with immune deficiency, one patient with tuberous sclerosis, and one patient with autoimmune hepatitis. 12 (40%) patients had no specific diagnoses and were lost to follow-up. In the hepatosplenomegaly group; 70% had thrombocytopenia, 63,3% had anemia, and 30% had leukopenia (Table 2).

Facial dysmorphism was seen in 15 patients; of which 3 patients had MPS, 2 patients had galactosialidosis, 1 patient had GM1 gangliosidosis, 1 patient had ISSD, and 8 patients did not have any specific diagnosis. Both weight SDS, and height SDS were lowest in the hepatosplenomegaly group but there was no statistically meaningful difference between the groups (p>0,05) (Table 1).

4 patients with non-immune hydrops fetalis were diagnosed as having Gaucher disease, NPC, galactosialidosis, ISSD, and two patients were undiagnosed. 3 patients with transient neonatal cholestasis were diagnosed with NPC. One NPC patient died with cholestasis and fulminant hepatic failure. The other 4 patients with neonatal cholestasis were diagnosed with MADD, ISSD, NPAB, and alpha-1 antitrypsin deficiency.

Since IEMs present with multisystemic involvement, neurological, ophthalmologic, and cardiac evaluations were also made. Neurological manifestations were observed in 2 patients with NPC, 2 patients with Gaucher disease, 2 patients with galactosialidosis, 2 patients with MPS, 1 patient with GM1 gangliosidosis, 1 patient with ISSD, 1 patient with NPAB, 1 patient with MADD, and 7 undiagnosed patients. One of the HM patients with MPS had mitral valve insufficiency, and another HM patient with galactosialidosis had mitral, and aortic valve insufficiencies. One patient with SM had mitral valve insufficiency whose diagnosis was Niemann-Pick disease type A/B. 5 patients with HSM had mitral valve insufficiency who were diagnosed as having sphingolipidosis. Cardiac rhabdomyoma was detected in a patient with tuberous sclerosis and HSM. Cherry-red spot was detected only in one patient with NPAB (Table 1). 4 patients with GSD also had renomegaly along with hepatomegaly.

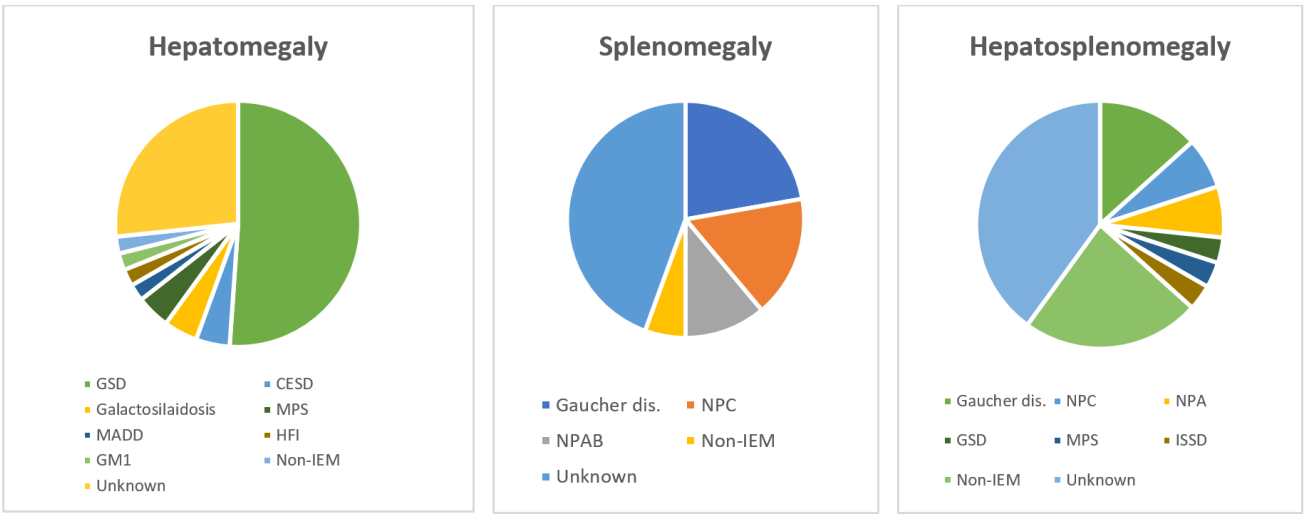

Figure 1. Specific diagnosis of patients according to type of visceromegaly
CESD: Cholesteryl-ester storage disease, dis.: Disease, GM1: GM1 gangliosidosis, GSD: Glycogen storage disease, HFI: Hereditary fructose intolerance, ISSD: Infantile Sialic Acid Storage Disease, MADD: Multiple Acyl-CoA dehydrogenase deficiency, MPS: Mucopolysaccharidosis, Non-IEM: Non-Inborn Errors of Metabolism, NPAB: Niemann-Pick disease type A/B, NPC: Niemann-Pick disease type C

On laboratory evaluation, 12 patients had hypoglycemia, and all were diagnosed with GSD. 58 patients had elevated liver enzymes, 43 of them had IEM. 12 patients had coagulopathy, 7 of them had IEM. 26 patients had hypercholesterolemia, and/or hypertriglyceridemia; 17 of them had GSD, 2 had CESD, 1 had MADD, one had immune deficiency, and 5 were undiagnosed. 12 patients had low HDL cholesterol levels; of which 6 had Gaucher disease, 2 had NPAB, 1 had NPC, 1 had familial HLH, and 2 were undiagnosed. 7 patients had hyperuricemia; diagnosis of 6 was GSD, and one was NPC. Elevated alpha-fetoprotein levels were detected in 16 patients, 3 had NPC, 2 had GDH, 1 had Gaucher disease, 1 had immune deficiency, 1 had alpha-1 antitrypsin deficiency, and 7 were without any specific diagnosis (Table 2). 18 patients had elevated acid phosphatase levels, 4 of them were without any diagnosis but 8 had Gaucher disease, 3 had NPC, 2 had galactosialidosis, and 1 had NPAB. 7 patients had elevated levels of biotinidase enzyme, 6 of them had GSD, and 1 was undiagnosed.

DISCUSSION

Hepatomegaly, splenomegaly, and hepatosplenomegaly are owing to either inherited or acquired etiologies in the pediatric population (1,2). Extensive diagnostic work-up for the specific diagnosis is needed in most cases. In the case that massive visceromegaly is present or the patient's general condition is not well, all the possible causes can be investigated simultaneously. For a patient with the possibility of having IEM, the exact diagnosis is crucial for providing the family genetic counseling. Diagnostic clues are needed to achieve this. In this study, patients in whom IEM diagnosis is anticipated, and referred to Pediatric Metabolism Department for evaluation were included. Unfortunately, regular patient follow-up was interrupted due to the COVID-19 pandemic, and a total of 32 patients were without a diagnosis and lost to follow-up. Another remarkable feature of our study population is that 43% of the patients were Syrian refugees. Considering high parental consanguinity rates, large family size, low socioeconomic status; IEMs tend to be more frequent in refugee children. Unfortunately, non-compliance to follow-up is more frequent in this group of patients.

Overall, a small number of patients (9,6%) had diagnoses other than an IEM. Probably, the reason is that these patients were referred to a pediatric metabolism specialist after certain etiological investigations, and only patients without a diagnosis were referred. Patients in this study had high rates of parental consanguinity (78,5%), and positive family history (34,4%), this is due to the high expectation of an underlying IEM in this group of patients. The most referrals in our study were from pediatricians. This may reflect an awareness of pediatricians for underlying IEM possibility of patients with visceromegaly. Patients without cytopenia were mostly referred from pediatric gastroenterologists, and patients with cytopenia were referred from pediatric hematologists. 2 patients' visceromegaly were noticed during neurological evaluation, and one patient with hepatomegaly and severe short

height was referred from the pediatric endocrinology department.

Half of the patients with hepatomegaly had been diagnosed with GSD. Accompanying findings such as short stature, hepatosteatosis, elevated liver enzymes, hyperlipidemia, low blood glucose, and hyperuricemia are important parameters to determine the underlying pathology. In a study evaluating 38 patients with GSD, all of the patients had hepatomegaly. Similarly, elevated liver function tests, hypoglycemia, hyperlipidemia, hyperuricemia were frequently observed (4). Other less often diagnoses were lipid storage diseases, fructose metabolism defects, and fatty acid oxidation defects (FAOD).

All the patients with splenomegaly were diagnosed with sphingolipidosis; namely Gaucher disease, NPAB, and NPC. Half of these patients had thrombocytopenia, and anemia probably due to hypersplenism. One-third of the patients had low HDL cholesterol levels. One patient had cherry-red spot. Cherry-red spot is a diagnostic but not a necessary finding in the matter of diagnosing sphingolipidosis. Except for one patient with GSD, all the patients with HSM had various lysosomal storage diseases. Non-IEM patients were most frequent in this group. Two-third of the patients had thrombocytopenia and anemia, and one-third of the patients had leukopenia. Short stature, neurological findings, elevated liver enzymes, coagulopathy, and elevated AFP levels were more prominent in this group. In the study from Denmark including primary evaluation of patients only with splenomegaly from all age groups, hematological diseases (39%) were the most common etiology followed by hepatic diseases (18%), and infections (10%). None of the patients had an IEM but the authors stated that in the prospective part of the study not all of the patients were evaluated regarding Gaucher disease1. Gaucher disease is an exemplary disease; early diagnosis, and timely treatment prevents irreversible clinical manifestations. First step in the diagnostic journey is adding the disease in the differential diagnosis. Radiological evaluations frequently aid the diagnosis. Radiographs may show Erlenmeyer flask deformity of the femur pointing to Gaucher disease or dysostosis multiplex in favor of lysosomal storage diseases (2,5). Liver steatosis can be observed in GSD, fructose, and galactose metabolism disorders, CESD, and other lipid storage diseases, FAOD or mitochondrial disorders, and splenic nodules or masses can be detected in Gaucher disease (2,6). Renomegaly is another finding of GSD (4). Four of our GSD patients also had renal enlargement.

CONCLUSION

Generally, clinical findings of inborn errors of metabolism are similar to other etiologies. Accordingly; diagnosis of IEMs is delayed, these patients are subject of exhaustive, and invasive diagnostic procedures such as bone marrow aspiration/biopsy, liver biopsy, and inappropriate or unnecessary treatments. Whereas, it is possible to simply diagnose these patients with enzyme analysis or genetic tests. IEMs do not only appear in the neonatal period or infancy but present from the prenatal period to adulthood. Thus, in the case of multisystemic involvement especially neurological involvement, and subacute or chronic clinical course clinicians should include IEMs in the differential diagnosis of visceromegaly. Awareness of clinicians should be raised, and diagnostic algorithms should be established to avoid misdiagnosis or unrecognition in this group of patients.

DECLARATIONS

Funding

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Conflicts of Interest/Competing Interests

Not applicable.

Ethics Approval

Ethical approval was obtained from Adana City Training, and Research Hospital Local Ethics Committee on 27.01.2021 with the document numbered 1266/75 for the study.

REFERENCES

1-Curovic Rotbain E, Lund Hansen D, Schaffalitzky de Muckadell O, Wibrand F, Meldgaard Lund A, Frederiksen H. Splenomegaly - Diagnostic validity, work-up,, and underlying causes. PLoS One 2017;12(11):e0186674. DOI: 10.1371/journal.pone.0186674

2-Sjoberg BP, Menias CO, Lubner MG, Mellnick VM, Pickhardt PJ. Splenomegaly: A Combined Clinical, and Radiologic Approach to the Differential Diagnosis. Gastroenterol Clin North Am 2018;47(3):643-66. DOI: 10.1016/j.gtc.2018.04.009

3-Konuş OL, Ozdemir A, Akkaya A, Erbaş G, Celik H, Işik S. Normal liver, spleen,, and kidney dimensions in neonates, infants,, and children: evaluation with sonography. AJR Am J Roentgenol 1998;171(6):1693-8. DOI: 10.2214/ajr.171.6.9843315.

4-Poojari V, Shah I, Shetty NS, Mirani S, Tolani D. Clinical profile, and outcome of glycogen storage disease in Indian children. Trop Doct 2021;51(2):189-92. DOI: 10.1177/0049475520961935

5-Oussoren E, Wagenmakers MAEM, Link B, van der Meijden JC, Pijnappel WWMP, Ruijter GJG, et al. Hip disease in Mucopolysaccharidoses, and Mucolipidoses: A review of mechanisms, interventions, and future perspectives. Bone 2021;143:115729. DOI: 10.1016/j.bone.2020.115729

6- Yıldız Y, Sivri HS. Inborn errors of metabolism in the differential diagnosis of fatty liver disease. Turk J Gastroenterol 2020;31(1):3-16. DOI: 10.5152/tjg.2019.19367