Original

Clinico-laboratory and histological characteristics in patients with gelatinous transformation of bone marrow

Sarina Takeuchi[*1], Mayuko Ichimura Shimizu*[*2], Satoshi Sumida*[*2],*
Koichi Tsuneyama[*2], Mai Kanai*[*3], Shunsuke Watanabe*[*4],*
Takahiko Kasai[*4], †Michiko Yamashita*[*3]*

†Correspondence: Department of Analytical Pathology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima-city, Tokushima 770-8503, Japan.
E-mail: yamashitar@tokushima-u.ac.jp
Received February 27, 2024; accepted December 9, 2024
*1 Department of Diagnostic Pathology, Tokushima Prefectural Central Hospital, 1-10-3, Kuramoto-cho, Tokushima-city, Tokushima 770-8539, Japan
*2 Department of Pathology and Laboratory Medicine. Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima-city, Tokushima 770-8503, Japan
*3 Department of Analytical Pathology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima-city, Tokushima 770-8503, Japan
*4 Department of Diagnostic Pathology, Japanese Red Cross Tokushima Hospital, 103, Irinokuchi, Komatsushima-cho, Komatsushima-city, Tokushima 773-8502, Japan

ABSTRACT

Gelatinous transformation (GT) is morphological change of fat tissue that reflects malnutrition. In bone marrow with GT, gelatinous deposits occupying hematopoietic space result in hypocellularity. Therefore, GT is presumed to be a cause of secondary anaemia. To characterise clinical feature, laboratory data and histology in patients with bone marrow GT, we enrolled 104 patients who were autopsied at Tokushima University Hospital and Tokushima Red Cross Hospital between August 2015 and July 2020. The patients were aged 71.7 ± 11.4 years (69.2% male individuals). Fifty-eight patients (55.8%) had malignant disease. Bone marrow and liver steatosis and medical records were retrospectively studied. Clinical data and basic blood and urine parameters prior to 3 weeks before death were analysed. Eighteen (17%) patients were assigned to the GT group. In this group, two (11.1%) cases were complicated by bone marrow fibrosis. Immunohistochemically, C-X-C motif chemokine ligand 12 (CXCL12) -positive stromal cells were present in the GT marrow area; however, the number of stellate-shaped reticular cells with projections strongly positive for CXCL12 was reduced. Statistically, GT was not associated with malignant disease, liver fibrosis, or steatosis. In the GT group, serum creatinine was significantly lower than that in the non-GT group (median 0.75 mg/dL, IQR 0.61–1.17, $p=0.047$). The body mass index and geriatric nutritional risk index were also significantly lower in the GT group (median 18.6, IQR 17.3–19.9, $p<0.001$; median 66.8, IQR 61.9–70.6, $p=0.002$, respectively). These results suggest that bone marrow GT indicates protein-energy malnutrition with muscle loss, but not with anaemia.

〔Lab Med Int 2025; 4(1): 34-45〕

Key Words
gelatinous transformation, serum creatinine, bone marrow

I. Introduction

Gelatinous transformation (GT) is known as a representative histologic finding related to malnutrition.[1)–3)] Synonyms for GT include "gelatinous degeneration" and "serous atrophy."[4)] Bone marrow with significant GT is called "gelatinous marrow" or "starvation marrow." In GT of the bone marrow, mucopolysaccharides rich in hyaluronic acid deposit around the fat cells and make the hematopoietic space narrow, leading to hypocellularity; therefore, GT is believed to be a finding of secondary anaemia.

In 2000, Böhm[3)] examined the underlying diseases in 155 cases of GT and identified the following causes: tumours (including hematologic malignancies and carcinomas), malnutrition (including alcoholism and anorexia nervosa), infections (including AIDS and active fevers), maldigestion (including stomach ulcers and post-gastrectomy), heart failure, metabolic disorders (including diabetes mellitus and hypothyroidism), and others. Weight loss or cachexia was found in 78% of the patients and 82% were anaemic. Böhm[3)] concluded that GT represents an indicator of severe illness in patients and that basic bioregulatory processes play a role in its pathogenesis.

However, most bone marrow examinations are performed in the presence of abnormal blood cell counts; thus, investigations using surgical material may have a bias towards anaemia. Many studies that consider anaemia as the basis for GT have been published;[3)5)6)] however, the correlation between GT and anaemia remains controversial.

The purpose of this study is to clarify the relationship between GT and organ failure and the type of PEM by retrospective observation. We also examined the status of hematopoiesis associated mesenchymal cells in GT bone marrow by immunostaining.

II. Materials and Methods

2. 1. Participants

Of the 205 patients who underwent autopsies at Tokushima University Hospital and Tokushima Red Cross Hospital between August 2015 and July 2020, 104 participants aged 18 years or older who had their bone marrow collected were enrolled (**Figure 1**). The enrolled participants' mean age was 71.7 ± 11.4 years and 69.2% were male. Fifty-eight (55.8%) patients had malignant disease, of whom 42 (40.4%) had solid tumours and 16 (15.4%) had haematolymphoid tumours. The exclusion criteria were patients for whom no laboratory data existed 3 weeks before autopsy and pathology specimens could not be prepared due to poor fixation and decalcification. This study was approved by the Ethics Committees of the University of Tokushima Hospital (Application No. 3869-2) and the requirement for informed consent was waived as no personal information was disclosed.

2. 2. Clinical data

Data on height, weight, clinical diagnosis, and autopsy diagnosis of malignancy at the last admission were collected.

3. 3. Laboratory data

Laboratory data 3 weeks before autopsy was obtained. The following blood laboratory parameters were evaluated: white blood cell, total neutrophil, total lymphocyte, red blood cell, and platelet counts; haemoglobin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, total bilirubin, total cholesterol, triglyceride, cholinesterase, albumin, total protein, globulin, creatinine, uric acid, and C-reactive protein levels; and the amount of urine protein and occult blood. For each test item, sample size calculation or power analysis was performed. Blood test data were evaluated based on previous studies on reference values for Japanese[7)].

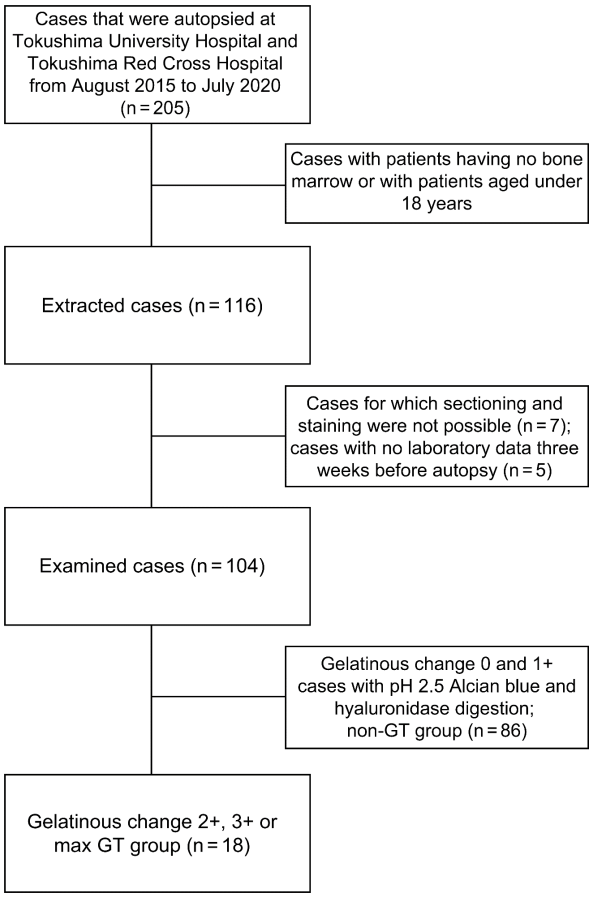

Figure 1 Trial profile. GT, gelatinous transformation.

2. 4. Calculation of nutrition indices

The body mass index (BMI)[8], prognostic nutritional index (PNI)[9], and geriatric nutritional risk index (GNRI)[10] were used as nutritional indices. The calculation formulae are as follows:

BMI = weight (kg)/ [height (m)]^2)

PNI = [10 × serum albumin (g/dL)] + [0.005 × Total lymphocyte count (/mm^3)]

GNRI = [14.89 × serum albumin (g/dL)] + [41.7 × (weight kg / ideal weight kg)]

*Formula for calculating ideal weight:

Male: height (cm)-100-[(height-150)/ 4]

Female: height (cm)-100-[(height-150)/ 2.5]

BMI was evaluated based on previous studies on reference values for Asians[11].

2.5.1 Assessment of bone marrow and liver pathology

Bone marrow specimens were sampled from the L1-2 level vertebra. Ethylenediaminetetraacetic acid decalcification was performed. Haematoxylin and eosin staining and pH 2.5 Alcian blue staining with the hyaluronidase digestion test were performed on thin sections of 10% formalin or 10% neutral buffered formalin-fixed paraffin-embedded blocks, along with the assessment of the percentage and extent of the areas of GT.

GT cases were recorded at five levels, as described in a previous study. The grading was as follows: Max, diffuse marrow involvement; 3+, large foci; 2+, focal lesions of intermediate size; 1+, single microfocal involvement; and 0, no involvement[3]. The degree of hypocellular marrow with hyaluronidase-reactive pH 2.5 Alcian blue-positive deposits was defined as 2+ or higher and divided into the gelatinous marrow group and the no-change group. Watanabe's silver impregnation staining was performed in cases where fibrosis was suspected.

For the assessment of liver pathology, two pathologists separately observed non-neoplastic area of haematoxylin-eosin-stained microscopic specimen to determine if there were significant steatosis.

2. 5. 2 Immunohistochemical study

All immunohistochemical staining was performed on formalin-fixed paraffin-embedded blocks tissue sections using a Histofine simple stain AP (R) kit and simple stain MAX-PO (M), followed by a new fuchsin substrate solution kit and a diaminobenzide solution kit (Nichirei Bioscience, Tokyo, Japan). The following primary antibodies were used: stromal cell-derived factor 1/CXCL12 and rabbit monoclonal (immunohistochemistry-specific) clone D8G6H, 1:300 (Cell Signaling Technology, Danvers, MA, USA) ; CD10, mouse monoclonal, clone 56C6; CD68, mouse monoclonal; and clone PG-M1 ready-to-use (Nichirei Bioscience, Tokyo, Japan).

2. 6. Statistical analyses

The characteristics of patients with and without GT were compared using the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Logistic regression analysis was used to assess the age- and sex-adjusted effect of each baseline characteristic: age, sex, malignancy, fatty or fibrous degeneration of the liver, and the presence of GT. Box and whiskers plots were used to evaluate median and interquartile ranges of each parameter. Statistical analyses were performed using R software version 4.2.1 (R Core Team, Vienna, Austria)[12].

III. Results

The baseline patient characteristics are shown in **Table 1.** Of the 104 participants enrolled, 18 (17%) were classified as having bone marrow GT. The histopathological findings and case distribution are shown in **Figure 2.** 15/18 (83%) patients had patchy GT lesions. Atrophy of fat cells and hypocellularity were observed within the GT area. There were two cases of bone marrow fibrosis coexisting with GT (**Figure 3**). In the complicated area, there was an increase in reticular cells, a mild increase in collagen fibres, and hyaluronidase digestion-reactive mucopolysaccharide deposition. Spindle cells in the fibrotic area were immunoreactive for CXCL12, CD10, and CD68.

CXCL12 is a chemokine that is widely expressed in a variety of stromal cells[13)-14)], reticulocytes expressing high levels of CXCL12 are called CXCL12-abundant reticular cells (CAR cells), which provide a haematopoietic environment for hematopoietic stromal cells and are themselves mesenchymal stem cells[15)-16)]. CAR cells were observed in various patterns, such as polygonal, stellate, spindle, and small round, and in the peri-adipose and peri-endothelial in normal (**Figure 4A**) and GT marrows (**Figure 4B, C, D**).

CD68 (PGM-1) is a specific marker for monocytes and histiocytes[17]. CD68 immunoreactive small round cells, mostly consistent with monocytes and stellate and spindle cells represented a part of the reticular cells and may have included CAR cells, and the giant cells were consistent with osteoclasts (**Figure 4E**).

CD10 is the enzyme primarily responsible for preadipocytes and adipocytes[18]. CD10 positivity was observed in the adipocytes. CD10 was also immunoreactive to spindle cells, consistent with some of the reticular cells and preadipocytes (**Figure 4F**).

CXCL12-CD68 co-expression in reticular cells was

Table 1 Baseline characteristics and comparison between the GT and non-GT groups

Item (unit)	N	GT group (N=18)	Non-GT group (N=86)	p-value[a]	Age-sex adjusted p-value
		n (%) or Median (IQR)			
Male sex	72	15 (83.3%)	57 (66.3%)	0.26	NA
Age (years)	104	76.0 [66.8–83.8]	71.5 [65.0–79.8]	0.2	NA
Malignancy	104	12 (66.7%)	46 (53.5%)	0.45	NA
Steatosis of the liver	103	9 (50.0%)	41 (48.2%)	1.00	NA
Fibrosis of the liver	103	7 (38.9%)	38 (44.7%)	0.85	NA
WBC count ($\times 10^9$/L)	104	9.26 [5.47–12.30]	11.92 [7.54–18.84]	0.15	0.10
Total neutrophil count ($\times 10^9$/L)	89	7.6 [4.10–9.60]	7.89 [3.63–14.68]	0.68	0.35
Total lymphocyte count ($\times 10^9$/L)	90	0.33 [0.23–0.74]	0.60 [0.34–0.89]	0.15	0.23
RBC count ($\times 10^{12}$/L)	104	3.08 [2.68–3.42]	3.12 [2.60–3.60]	0.85	0.91
Hemoglobin level (g/L)	104	92 [83.8–106.5]	95 [77.0–114.0]	0.99	0.68
Platelet count ($\times 10^9$/L)	104	154.0 [82–168.5]	117.5 [32–211.5]	0.31	0.84
Aspartate aminotransferase level (IU/L)	100	31.0 [21.8–64.3]	53.5 [25.0–133.5]	0.19	0.49
Alanine transaminase level (IU/L)	99	24.5 [10.5–51.3]	34.0 [15.5–65.5]	0.20	0.54
Alkaline phosphatase level (IU/L)	93	423 [217.3–1121.8]	379 [253.5–690.5]	0.59	0.039
Gamma-glutamyl transpeptidase level (IU/L)	94	94 [17.5–294.3]	68 [35.3–147.3]	0.84	0.36
Cholinesterase level (IU/L)	11	106 [86–126]	114 [100–179]	0.73	0.45
Total bilirubin level (mg/dL)	97	0.7 [0.6–2.6]	1.1 [0.6–2.7]	0.53	0.35
Total bilirubin level (μmol/L)		12.0 [10.3–44.5]	18.8 [10.3–46.1]		
TC level (mg/dL)	13	184 [119–249]	142 [118–156]	1.00	0.49
TC level (mmol/L)		4.76 [3.08–6.44]	3.67 [3.05–4.03]		
TG level (mg/dL)	10	48 [48–48]	92 [84–114]	0.20	1.00
TG level (mmol/L)		0.54 [0.54–0.54]	1.04 [0.95–1.29]		
Albumin level (g/L)	89	19 [18–24]	23 [19–28]	0.058	0.066
Total protein level (g/L)	67	48 [44–55]	55 [48–61]	0.095	0.19
Globulin level (g/L)[b]	67	28 [26–33]	29 [25–36]	0.89	0.93
Creatinine level (mg/dL)	98	0.75 [0.61–1.17]	1.42 [0.71–2.51]	0.047	0.085
Creatinine level (μmol/L)		66.3 [53.9–103]	126 [62.8–222]		
Creatinine level 3 weeks before death (mg/dL)	50	0.60 [0.49–0.74]	0.86 [0.64–1.24]	0.009	0.042
Creatinine level 3 weeks before death μmol/L)		53.0 [43.3–65.4]	76.0 [56.6–109]		
Uric acid level (mg/dL)	39	5.5 [4.0–8.3]	6.4 [4.5–8.56]	0.84	0.74
Uric acid level (μmol/L)		327 [238–494]	381 [268–509]		
CRP level (mg/dL)	99	7.3 [2.9–15.1]	6.1 [2.7–13.2]	0.94	0.52
CRP level (ug/L)		73000 [29000–151000]	61000 [27000–132000]		
Urine protein qualitative	33			0.44	0.51
−		0 (0%)	1 (3.3%)		
±		1 (33.3%)	6 (20%)		
1+		2 (66.7%)	15 (50%)		
2+		0 (0%)	5 (16.7%)		
3+		0 (0%)	3 (10%)		
Urine occult blood qualitative	33			0.42	0.56
−		1 (33.3%)	8 (26.7%)		
±		0 (0.0%)	3 (10.0%)		
1+		2 (66.7%)	6 (20.0%)		
2+		0 (0.0%)	11 (36.7%)		
3+		0 (0.0%)	2 (6.7%)		
BMI (kg/m^2)	90	18.6 [17.3–19.9]	21.9 [19.7–24.3]	<0.001	0.004
PNI (kg/m^2)	75	23.0 [19.6–27.4]	26.3 [22.0–33.4]	0.035	0.066
GNRI (kg/m^2)	76	66.8 [61.9–70.6]	75.9 [71.2–89.5]	0.002	0.007

GT, gelatinous transformation; IQR, interquartile range; WBC, white blood cell; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; CRP, C-reactive protein; BMI, body mass index; PNI, prognostic nutritional index, GNRI, geriatric nutritional risk index.
* aMann–Whitney U tests were used for continuous variables; Chi-square tests were used for categorical variables. † bGlobulin: (Total protein)-(Albumin).

observed in the hematopoietic area, although the co-expressed stellate cells decreased in the GT area. Reticular cells with CXCL12-abundant long projections were consistent with CAR cells (**Figure 5**). These findings suggested that CAR cells, as mesenchymal stem cells, differentiate into fibroblasts, monocytes, macrophages, and adipocytes in the altered bone marrow, leading to hypocellularity.

A comparison between the GT and non-GT groups is presented in **Table 1.** GT was not significantly correlated to age or sex, nor presence or absence of malignancy. Both the GT and non-GT groups were anaemic; RBC (3.08 vs 3.12 10^{12}/L [male 4.35-5.55, female 3.86-4.92]), Haemoglobin (92 vs 95 g/L [male 137-168, female 116-148]), and had increased white blood cell counts and positive CRP levels (7.3 vs 6.1 mg/dL, 73000 vs 61000 μg/L), but there were no significant differences.

Fatty degeneration of the liver was observed in nearly

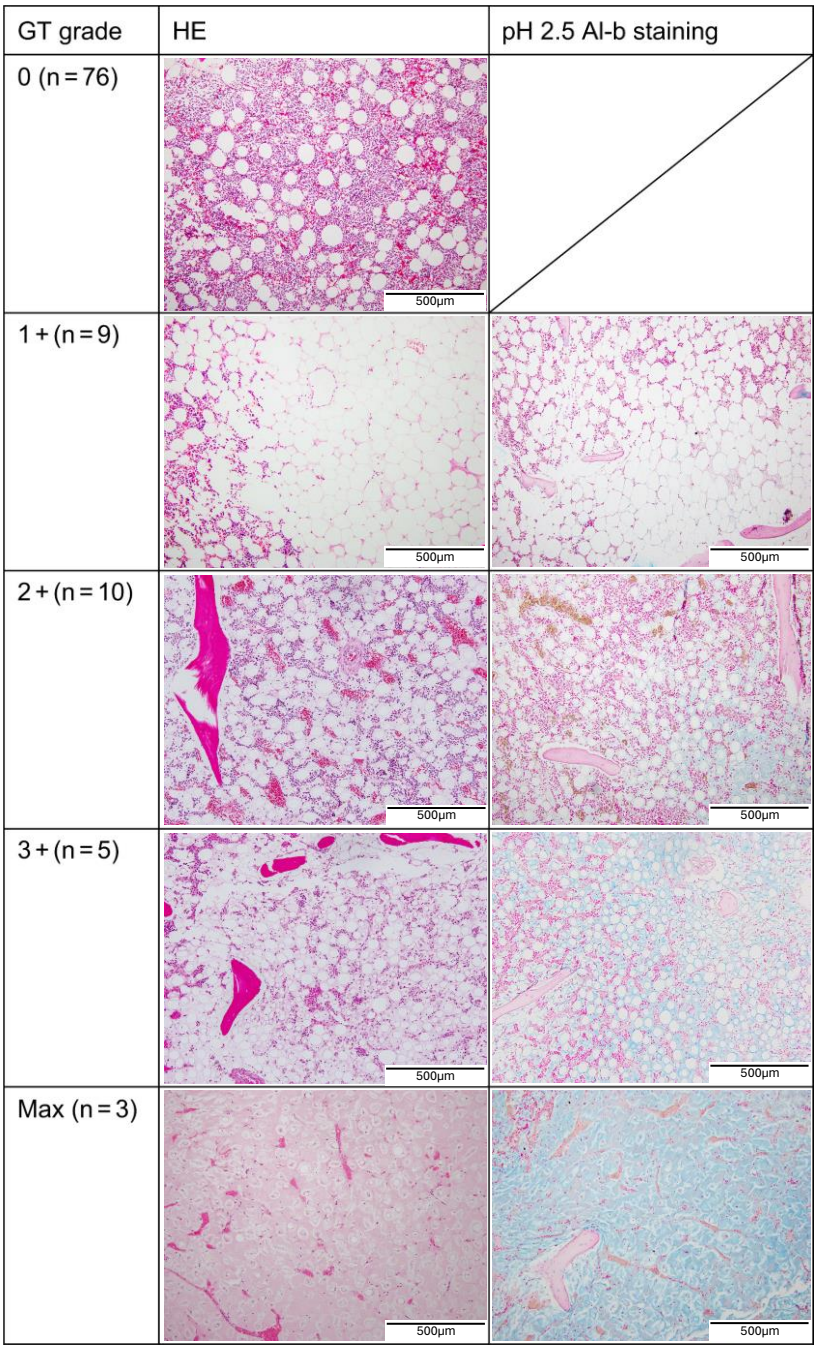

Figure 2 Histological grading of gelatinous transformation (scale bar=200 μm).
GT areas are patchily distributed in most cases. HE, haematoxylin-eosin staining; Al-b, pH 2.5 Alcian blue staining; GT, gelatinous transformation.

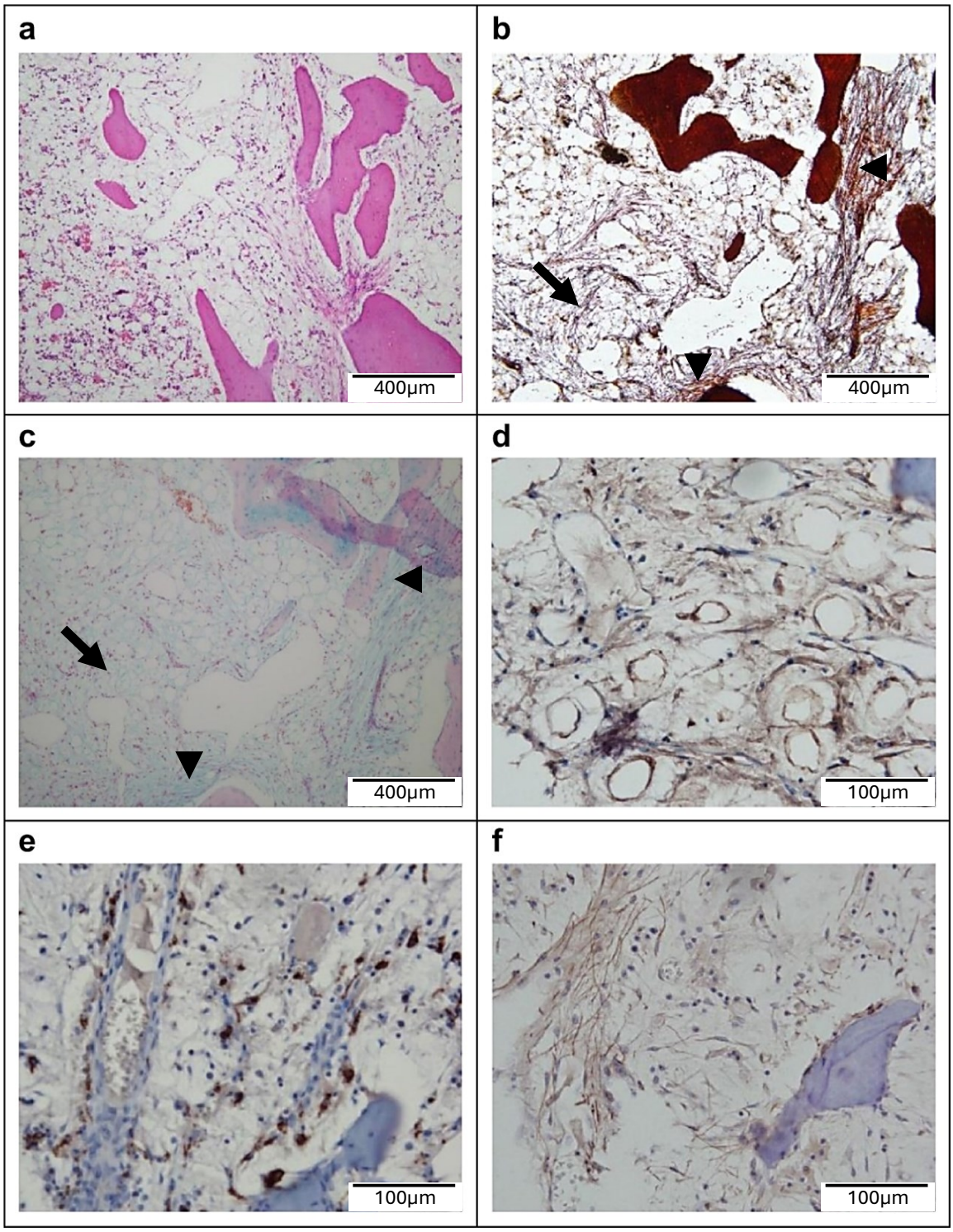

Figure 3 Microscopic findings of GT with fibrosis cases (A: scale bar=100 μm, B−F: scale bar=50 μm).
A. Haematoxylin-eosin staining. Bone and fibrous materials are increased. B. Silver impregnation staining. Brown-black reticular fibres (arrows) and brown-red collagen fibres (arrowheads) are increased. C. pH 2.5 Alcian blue staining. Blue colour is observed in both the GT and fibrotic area. These are both-hyaluronidase reactive. B, C. Serial sections. Bone tissue is displaced by sectioning artifacts. D. CD10-immunohistochemistry (IHC). A few spindle cells and fat cells show positivity. E. CD68-IHC. Monocytes, macrophages, periosteal giant cells, and some spindle cells are immunoreactive for CD68. F. CXCL12-IHC. The fibre-like projection of some spindle cells in fibrosis is positive. CXCL12, C-X-C motif chemokine ligand 12; GT, gelatinous transformation.

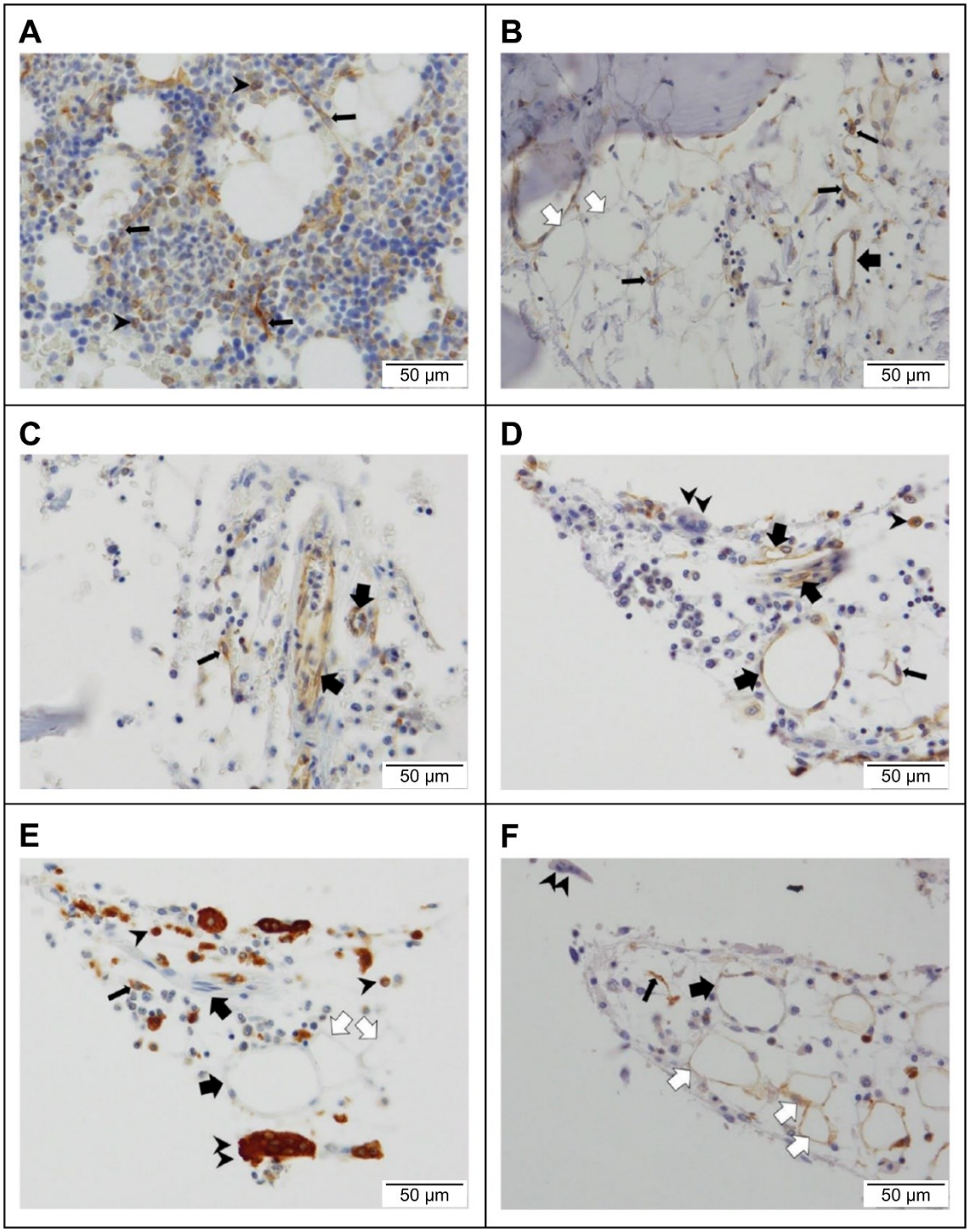

Figure 4 Immunohistochemical findings of GT marrow (scale bar=50 μm).
A: CXCL12-immunohistochemistry (IHC) in normal control. CXCL12 immunoreactive small round cells (arrowheads) and stellate cells are seen. Long projections of stellate cells among hematopoietic cells are strongly positive (arrows). These may be CAR cells. B–D: CXCL12- IHC in the GT marrow. B, C: CXCL12 positivity is observed in spindle cells (small black arrows), peri-adipose cells (white arrows), and peri-endothelial (black arrows). D: CXCL12 positivity is observed in small round cells (arrowhead), spindle cells (small black arrow), and peri-endothelial area (black arrows), but not for giant cells (double arrowheads). E: CD68-IHC in the GT marrow. Small round cells (arrowheads), spindle cells (small black arrow), and giant cells (double arrowheads) were immunoreactive. The peri-endothelial area (black arrows) and adipose cells (white arrows) were not reactive for CD68. F: CD10-IHC in the GT marrow. Fat cells (white arrows) and spindle cells (small black arrow) are immunoreactive but are not reactive for the peri-endothelial area (black arrows), giant cells (double arrowhead). D–F are complete serial sections. Bone tissue around the bone marrow tissue is off-screen due to sectioning artifacts. CXCL12, C-X-C motif chemokine ligand 12; CAR cells, C-X-C motif chemokine ligand 12-abundant reticular cells; GT, gelatinous transformation.

half of the patients in both groups, seemed to suggest steatohepatitis due to nutritional disorders, but there was no significant difference between the two groups. In both groups, Gamma-glutamyl transpeptidase level was above the reference range [male13-64, female 9-32], but median total bilirubin remained in the reference standard range [0.4-1.5mg/dL, 6.8-26.3μmol/L]. Median ALT, suggestive of hepatocellular damage, was slightly higher than the reference range [24.5 vs 34.0 IU/L male10-42, female 7-23 IU/L], reflecting organ damage immediately before death, but was lower in the GT group than in the non-GT group, with no significant difference between the two groups [24.5 vs 34.0 IU/L].

Median serum creatinine (sCr) in the non-GT group was high (1.42 mg/dL [male 0.66-1.06, female 0.46-0.79]; 66.3 vs. 126 μmol/L [male 72.7-109.1, female 54.5-81.8]). reflects various renal dysfunctions immediately prior to death, while median sCr in the GT group was in

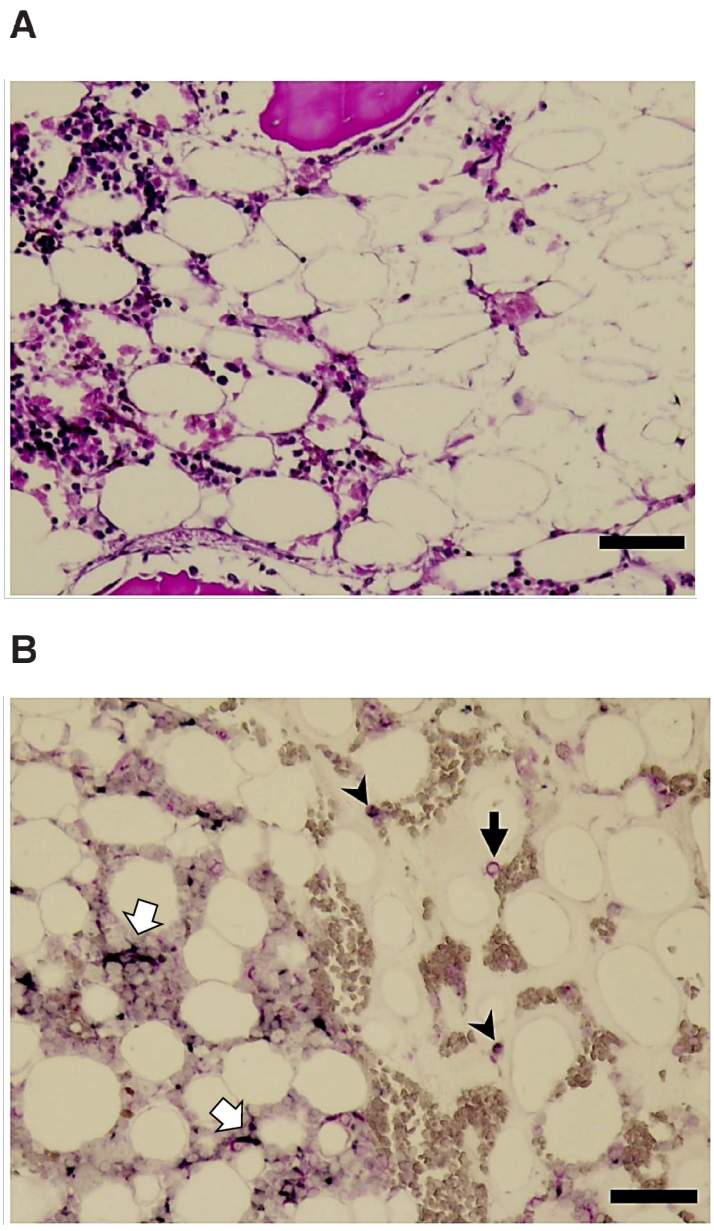

Figure 5 Double-immunostaining results for CXCL12 and CD68 in GT (scale bar=100 μm).
A: Haematoxylin-eosin staining of GT marrow. The left half is the normocellular area, and right half is the patchy GT area. B. CXCL12 (red) CD68 (blue black) double immunostaining in the GT marrow. Stellate reticular cells that express CXCL12 in long projections and CD68 in cytoplasm (white arrows) are seen in the normocellular area. Reticular cells have shortened CXCL12-positive projections (arrowheads), and CXCL12-positive small round cells (black arrow) are observed in the GT area. CXCL12, C-X-C motif chemokine ligand 12; GT, gelatinous transformation.

the reference range (0.75 mg/dL, 66.3 μmol/L). The GT group also had significantly lower sCr levels than the non-GT group (p=0.047). The sCr level 3 weeks before death are significantly lower in GT group, after adjusting the age- and sex (p=0.042).

Both groups had low median albumin level (19 vs. 23 g/L [41-51]) and The GT group tended to have lower albumin than the non-GT group (p=0.066). Similarly, both groups had lower BMI (18.6 vs. 21.9 kg/m^2 [22.6-27.5]), and GNRI (66.8 vs.75.9 kg/m^2), but the GT group had significantly lower BMI and GNRI than the non-GT group (p<0.001 and p=0.002, respectively). The exact data are shown in **Figure 6**.

IV. Discussion

We investigated GT marrow at autopsy and found that

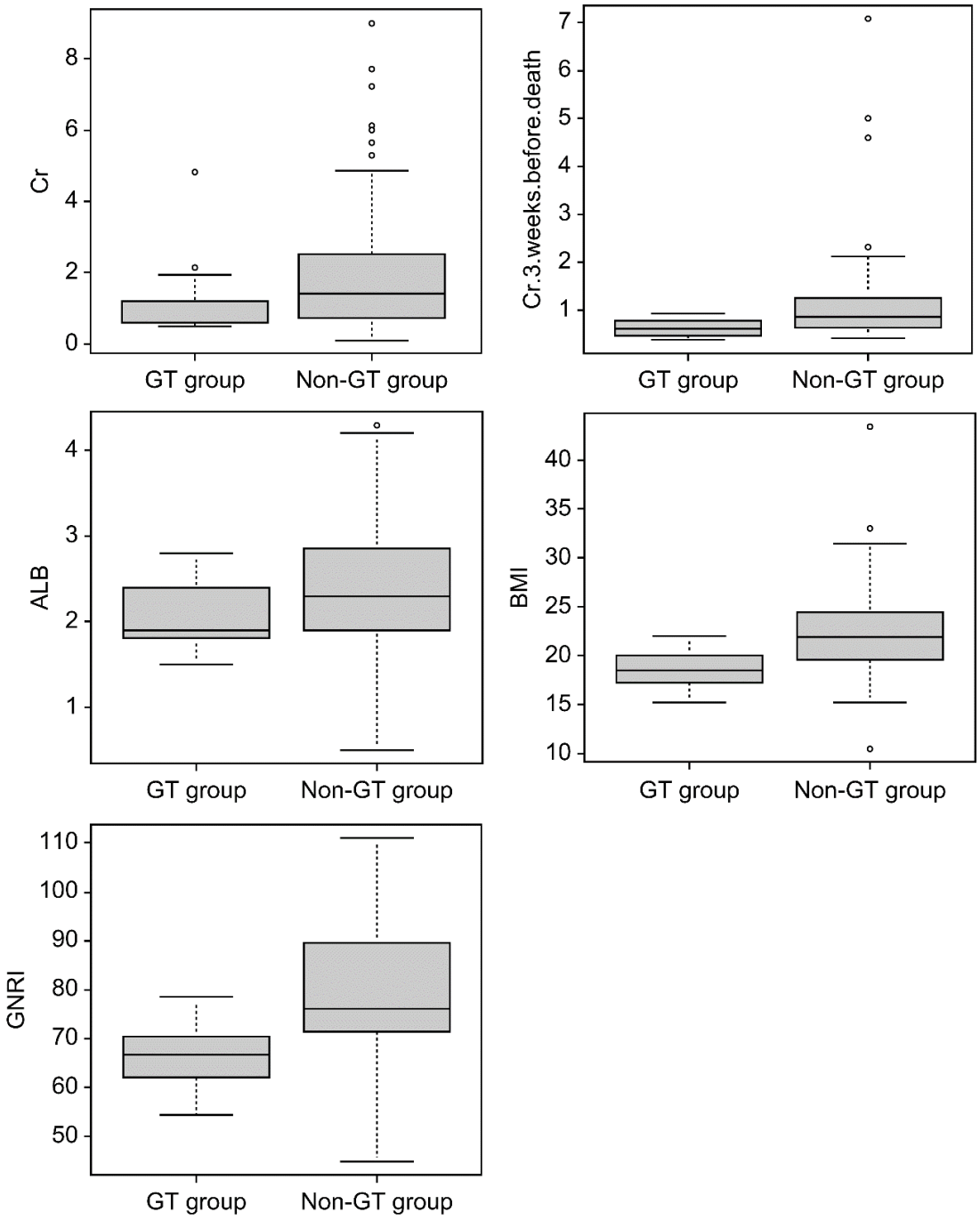

Figure 6 Comparison of each parameter between GT and non-GT groups.
GT, gelatinous transformation; BMI, body mass index; GNRI, geriatric nutritional risk index; Cr, creatinine; ALB, albumin.

the GT area had different reticular cell conditions. And our analysis of clinico-laboratory data of GT and non-GT patients. As previously hypothesized, we confirmed a strong association with malnutrition; however, unlike previous hypotheses [1)-6)], there was weak association with anaemia. Furthermore, we reported interesting phenomenon that the sCr of the GT patients remained in the reference range, even just before death.

We speculated that the significantly lower sCr levels had been observed in the GT group from 3 weeks prior form death were related to the presence of muscle loss. Recently low sCr "on admission" has been theorized to be related to sarcopenia when other causes can be ruled out [19)-24)]. Our series do not have patients with fluid excess condition, myoneuropathy, paralysis or limb amputation. Liver dysfunction was negative in the data analysis, suggesting muscle reduction as a possible cause.

Nutrition indicators, both groups had low median BMI, but the GT group had a median value below 2.0 kg/m^2, which is a poor prognosis for life [25)-26)]. Protein-energy malnutrition (PEM) is the condition of lack of energy due to the deficiency of all the macronutrients and many micronutrients [27)]. in recent years, PEM is known as the main cause of sarcopenia; defined as a progressive and generalized skeletal muscle disorder involving the accelerated loss of muscle and its function [28)-29)]. In children, marasmic kwashiorkor phenotypes are also present [26) 30)-31)], but in adults, which are more common in nutritional disorders in developed countries, there are two major types of PEM: marasmus/cachexia, and kwashiorkor/protein-calorie malnutrition (PCM) [27)]. Marasmus/cachexia is balanced malnutrition caused by long-standing starvation or chronic systemic inflammation. The prognosis for marasmus/cachexia is relatively good, although it involves substantial loss of body mass, with body weight less than 80% of the standard for height [26)-27)]. Thus, low BMI in our GT group represents marasmus/cachexia. In contrast, kwashiorkor/PCM is caused by loss of relative protein intake. In 1933, Williams reported kwashiorkor in children in the Gold Coast of West Africa. Kwashiorkor fatality was as high as 90% and fatty change of the liver was observed in autopsy [27) 30)-31)]. In developed countries, kwashiorkor/PCM may occur within weeks of subsequent acute life-threatening illnesses, such as trauma and sepsis. The patients look well-nourished because of systemic oedema; however, their blood shows hypoalbuminemia and lymphocytopenia. Under stressed conditions, patients with kwashiorkor/PCM show hypermetabolism with high cytokine levels, such as tumour necrosis factor alpha, interleukin-1, and interleukin-6 and high stress hormone levels, such as catecholamine, glucagon, and cortisol, which leads to proteolysis and absolute fat catabolism, poor wound healing, and impaired host deficiency [26)]. Considering the significantly lower albumin and higher CRP levels in the GT group, it is likely that the GT have a severe condition of anabolic failure as seen in kwashiorkor/PCM.

In the GT group, except in a small number of maximal cases, the bone marrow hypocellularity associated with GT was patchily distributed and haematopoietic area remained. We consider this histological feature reflects the low association between GT and anaemia. In the GT area, various morphologies of CXCL-12 positive mesenchymal cells co-expressed multiple mesenchymal molecules, such as CD10 or CD68 and CXCL12-abundant projections were less observed. We estimate this histological finding implies CAR cells differentiation and haemopoietic cell depletion [32)]. Like GT, Mucopolysaccharide accumulation in deep connective tissue is often observed in myxoedema, a thyroid hormone dysregulation [33) 34)]. However, the mechanisms and histology of the dysthyroid status have not been adequately reported. The trends in clinical data that were significant in the GT group patients in this study appear to have much in common with thyroid hormone abnormalities, particularly the low T3 syndrome (also known as non-thyroidal disease syndrome).[35)] It would be beneficial to consider the common features of GT with the low T3 syndrome.

A limitation of this study is that the required sample size was not met. The study design, a retrospective observational study, resulted in many missing items like hormone test values. Also, we could not obtain good staining results due to damage from specimen decalcification. we should have performed immunostaining for many bone marrow mesenchymal markers such as leptin, CD163, and adipophilin, but we could not obtain good staining results due to damage from specimen decalcification.

In conclusion, 17% of autopsy adult cases had overt GT; 83% had patchy progression. Mesenchymal cells in the GT region co-expressed multiple molecules. Bone marrow GT was associated with low BMI, GNRI, and low sCr level. These results suggest that bone marrow GT is associated with PEM with muscle loss, but not with anaemia.

Acknowledgment

We would like to thank Professor Ayumi Shintani of Osaka Metropolitan University for organizing the Statistics for Research Skills seminar through the Awa Support Centre.

Funding

None.

Authorship Contributions

ST, MY, and TK collected laboratory data and performed statistical analysis; MY supervised the study and analysed bone marrow histopathology; MIS reviewed and interpreted nutritional indices; SS and KT analysed liver histopathology; and MK, ST, and SW prepared pathology specimens. All authors read and approved the final paper.

Disclosure of Conflict of Interest

The authors declare no conflict of interest.

References

1) Michael P. Gelatinous degeneration of the bone marrow. J Pathol 1930; 33 (3): 533-8.
2) Mills SE. Histology for pathologists. 5th ed. Wolters Kluwer; 2019.
3) Böhm J. Gelatinous transformation of the bone marrow: the spectrum of underlying diseases. Am J Surg Pathol 2000; 24 (1): 56-65.
4) Seaman JP, Kjeldsberg CR, Linker A. Gelatinous transformation of the bone marrow. Hum Pathol 1978; 9 (6): 685-92.
5) Shergill KK, Shergill GS, Pillai HJ. Gelatinous transformation of bone marrow: rare or underdiagnosed? Autops Case Rep 2017; 7 (4): 8-17.
6) Sen R, Singh S, Singh H, et al. Clinical profile in gelatinous bone marrow transformation. J Assoc Physicians India 2003; 51: 585-8.
7) Ichihara K, Yamamoto Y, Hotta T, et al. Collaborative derivation of reference intervals for major clinical laboratory tests in Japan. Ann Clin Biochem 2016; 53 (Pt 3): 347-56.
8) Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. Nutr Today 2015; 50 (3): 117-28.
9) Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi 1984; 85 (9): 1001-5.
10) Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005; 82 (4): 777-83.
11) Zheng W, McLerran DF, Rolland B. et al. Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians. N Engl J Med 2011; 364 (8):719-29.
12) R: A Language and Environment for Statistical Computing [Internet]; 2022. [cited 2022.12.1]. Available from: https://www.R-project.org/. Vienna: R Core Team.
13) Nagasawa T, Hirota S, Tachibana K, et al. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. Nature 1996; 382 (6592): 635-8.
14) Sugiyama T, Kohara H, Noda M, et al. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 2006; 25 (6): 977-88.
15) Prasad P, Cancelas JA. From Marrow to Bone and Fat: Exploring the Multifaceted Roles of Leptin Receptor Positive Bone Marrow Mesenchymal Stromal Cells. Cells 2024; 13 (11): 910.
16) Omatsu Y, Aiba S, Maeta T, et al. Runx1 and Runx2 inhibit fibrotic conversion of cellular niches for hematopoietic stem cells. Nat commu 2022; 13 (1): 2654.
17) Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; 36 (7): 1703-19.
18) Ding L, Vezzani B, Khan N, et al. CD10 expression identifies a subset of human perivascular progenitor cells with high proliferation and calcification potentials. Stem Cells 2020; 38 (2): 261-75.
19) Lien YHH. Looking for sarcopenia biomarkers. Am J Med 2017; 130 (5): 502-3.
20) Park J, Mehrotra R, Rhee CM, et al. Serum creatinine level, a surrogate of muscle mass, predicts mortality in peritoneal dialysis patients. Nephrol Dial Transplant 2013; 28 (8): 2146-55.
21) Schutte JE, Longhurst JC, Gaffney FA, et al. Total plasma creatinine: an accurate measure of total striated muscle mass. J Appl Physiol Respir Environ Exerc Physiol 1981; 51 (3): 762-6.
22) Thongprayoon C, Cheungpasitporn W, Kashani K. Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients. J Thorac Dis 2016; 8 (5): E305-11.
23) Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014; 15 (2): 95-101.
24) Cruz-Jentoft AJ, Baehens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European working group on sarcopenia in older People. Age Ageing 2010; 39 (4): 412-23.
25) Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015; 50 (3): 117-28.
26) Grover Z, Ee LC. Protein energy malnutrition. Pediatr Clin North Am 2009, 56 (5): 1055-68.
27) Heimburger DC. Malnutrition and nutritional assessment. Harrison's principles of internal medicine, 18th ed. McGraw-Hill Professional 2011; 605-11.
28) Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019; 393 (10191): 2636-46.

29) Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle 2016; 7 (5) : 512-4.
30) Williams CD. A nutritional disease of childhood associated with a maize diet. Arch Dis Child 1933; 8 (48) : 423-33.
31) Williams CD, Oxon BM, BRCP, et al. Kwashiorkor, A nutritional disease of children associated with a maize diet. Lancet 1935; 226 (5855) : 1151-2.
32) Omatsu Y, Nagasawa T. Identification of microenvironmental niches for hematopoietic stem cells and lymphoid progenitors–bone marrow fibroblastic reticular cells with salient features. Int Immunol 2021; 33 (12) : 821-6.
33) Elshimy G, Chippa V, Correa R. Myxedema. StatPearls [Internet]. Treasure Island (FL) : StatPearls Publishing; 2024. Last Update: August 14, 2023.
34) Rongioletti F, Rebora A. Cutaneous mucinoses: microscopic criteria for diagnosis. Am J Dermatopathol. 2001; 23 (3) : 257-67.
35) Fliers E, Bianco AC, Langouche L, et al. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol, 2015; 3 (10) : 816-25.