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DONOR-DERIVED MYELOID SARCOMA IN A KIDNEY TRANSPLANT RECIPIENT: CLINICAL CASE STUDY AND RELEVANCE OF A MULTIDISCIPLINARY APPROACH IN THERAPY AND DIAGNOSIS

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Background. Malignant tumors are one of the main causes of unfavorable outcomes in solid organ transplant recipients in the long term after transplantation. Localization of these tumors in a transplanted organ may cause loss of graft function. After chronic graft dysfunction and infections, malignant neoplasms come next as one of the leading causes of late kidney graft loss. The incidence of different types of malignancies varies according to the transplanted organ. Knowledge of etiology, pathogenesis, peculiarities of diagnosis and treatment of malignant tumors in solid organ transplant recipients is a significant part of screening at any stage of post-transplant period. Late diagnosis of malignancies in a transplanted kidney amidst disconnected stages of treatment and follow-up leads not only to graft loss, but also jeopardizes the life of recipients. **Clinical case description.** The patient is a 29-year-old female. History: IgA nephropathy with nephrosclerosis. Renal replacement therapy (RRT) with long-term hemodialysis since March 2019. Kidney transplantation from a deceased donor to the right external iliac vessels on March 13, 2019. Graft function is immediate. In October 2020, a tumor in the transplanted kidney was detected for the first time. In November 2021, an emergency graft nephrectomy was performed for health reasons. Antibacterial, antifungal therapy was carried out. Results of morphological study of the removed renal graft with immunohistochemistry (IHC) were obtained. The structure and phenotype of the tumor are consistent with myeloid sarcoma. Trephine biopsy: normocellular bone marrow. **Conclusion.** The 29-year-old patient was diagnosed with donor-derived myeloid sarcoma in her kidney transplant with the development of paraneoplastic syndrome and multi-organ failure. Currently, the patient is receiving RRT by long-term scheduled hemodialysis. Organ recipients need to be managed by a multidisciplinary team of specialized and highly specialized specialists, taking into account comorbid status and features of the course of the underlying disease.

Keywords: myeloid sarcoma, kidney transplantation, chronic kidney disease, immunohistochemistry, pathomorphology, oncohematology.

INTRODUCTION

After chronic graft dysfunction and infections, malignant tumors come next as one of the leading causes of late kidney graft loss, accounting for about 10% [1]. Most often, these are post-transplant lymphoproliferative disorders and kidney cancer, but, of course, other tumor localizations are not ruled out [2]. The risk of carcinogenesis in transplant recipients is significantly higher than in the general population due to the loss of immunological supervision over the appearance and proliferation of atypical cells against the background of immunosuppressants. Posttransplant malignancies are thought to develop by three mechanisms: *de novo* development, donor-related transmission, and recurrence of a recipient's pretransplant malignancy. Although nonmelanoma skin cancer, Kaposi sarcoma, posttransplant lymphoproliferative disorder, anogenital cancer, and lung cancer are malignancies that are thought to arise *de novo*, malignant melanoma and cancers that arise in the renal allograft are frequently donor related [3]. Nonmelanoma skin cancer, lip cancer, post-transplant lymphoproliferative disorders and anal cancer have the highest incidence in the organ recipient population. The incidence of different types of malignancies varies depending on the organ transplanted [4].

The incidence of myeloid sarcoma in patients after kidney transplantation is very rare, with only a few cases described in the world literature [5–10].

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Myeloid sarcoma (extramedullary myeloid tumor, granulocytic sarcoma, chloroma) is a tumor composed of myeloid progenitor cells arising anywhere other than the bone marrow (most commonly in the skin, lymph nodes, gastrointestinal tract, bones, soft tissues, and testes). Myeloid sarcoma may develop *de novo*, preceding acute myeloid leukemia (AML), parallel to the development of AML, or manifest as a blast transformation of myelodysplastic syndrome, a myeloproliferative disorder. Diagnosis is based on tumor biopsy and further use of cytochemical and immunohistochemistry (IHC) methods. Sarcoma in the general population occurs in 2.5–9.11% of AML patients [11]. Isolated myelosarcoma, without bone marrow involvement, is extremely rare (less than 1% of cases) [12]. The misdiagnosis rate is 75%, and 25–47% when IHC is used [13–15].

It is worth noting that traditional cytogenetic analysis in myeloid sarcoma is rarely performed because it is often mistaken for a solid tumor at the time of diagnosis, and samples suitable for cytogenetic analysis are not collected. Most data on genomic abnormalities are derived from individual case reports and karyotyping of the corresponding bone marrow, whereas myeloid sarcoma samples have been tested for targeted abnormalities using fluorescence in situ hybridization (FISH) [16]. Complete concordance between FISH and conventional cytogenetic results has been reported in only 71% of evaluable patients [17]. This suggests that conventional cytogenetic studies of both bone marrow and peripheral blood blasts (if available) and FISH analysis of myeloid sarcoma cells are complementary and should be performed in a clinical setting. In isolated myeloid sarcoma, FISH or conventional cytogenetic analysis of freshly obtained sarcoma cells is recommended [18].

CLINICAL OBSERVATION

A 29-year-old female patient with a long history of IgA nephropathy with outcome in nephrosclerosis, which required the start of renal replacement therapy (RRT) with long-term hemodialysis from March 2019.

Kidney transplantation from a deceased donor to the right external iliac vessels was performed at the transplant center of the Siberian Federal District on March 13, 2019. Graft function was immediate. Induction therapy included basiliximab and methylprednisolone. In the postoperative period, immunosuppressive therapy with cyclosporine, mycophenolic acid, methylprednisolone was used. The patient was discharged to the outpatient stage at her place of residence, in the Far Eastern Federal District, where she was observed by a nephrologist. The frequency of examinations and their volume at the place of residence are unknown. The patient did not keep in touch with the specialists of the center where the transplantation was performed. The outpatient follow-up data are not presented in full. Based on the provided documentation, it is known that in October 2020, the patient complained of pain in the graft area, liquid stools, and general weakness. An ultrasound that was performed at the patient's place of residence, detected, for the first time, a hypoechoic mass in the lower third of the transplanted kidney, measuring 23 × 29 mm in size (not classified according to Bosniak by the specialists at the place of residence). Taking into account laboratory examination and MRI data (the protocol was not provided), the detected changes were interpreted by the supervising nephrologist as graft pyelonephritis. Ertapenem-based antibiotic therapy was administered with a pronounced positive effect. Given the stable laboratory parameters, dynamic follow-up tactics were chosen. At subsequent irregular ultrasound screenings, a mass in the transplanted kidney was considered by specialists as a cyst.

In September 2021, MRI detected in the lower pole an enlarged mass of irregular round shape with unclear, uneven contours, a heterogeneous structure (due to the presence of areas of necrosis and cystic inclusions), 63 × 66 mm in size with heterogeneous accumulation of contrast agent. The level of azotemia during this period was unknown.

Following this, a biopsy of the transplanted kidney mass was performed at the patient's place of residence on October 11, 2021. Based on the results of histological examination of the biopsy specimen, the presence of a lymphoproliferative disorder was ruled out. IHC was not performed due to insufficient amount of material.

For further examination and treatment, in November 2021 the patient on her own came to Petrov National Medical Research Center for Oncology, St. Petersburg. A revision of morphologic preparations identified the pattern and immunophenotype of infiltrate from hematopoietic cells. Within the available biopsy, taking into account clinical data and negativity to many linear markers, one cannot categorically differentiate reactive inflammatory infiltrate and lymphoproliferative disorder. A more accurate differential diagnosis can be made on a more voluminous material.

At the same time, the patient felt worse, complaining of decreased diuresis. There was increased azotemia at the pre-hospital stage, which was detected during consultations at the Petrov National Medical Research Center for Oncology. On November 2, 2021, the patient was urgently hospitalized in a non-core hospital in St. Petersburg, where percutaneous nephropyelostomy of the transplanted kidney was performed due to graft hydronephrosis. Post-renal acute kidney injury (AKI) was diagnosed. Positive clinical and laboratory dynamics were achieved against the background of treatment. During this hospitalization, it was decided to perform repeat fine-needle percutaneous renal biopsy of the graft mass. The postoperative period was complicated by the formation of abdominal wall hematoma. Antibacterial

therapy and red blood cell transfusions were performed. The patient was discharged from the hospital at her own request on November 11, 2021.

On the same day, due to progressive deterioration in her condition, the patient, on her own, came to the kidney transplant department of Pavlov University.

The results of repeat biopsy of the kidney transplant mass (on November 8, 2021) were in progress at the time of admission.

On examination: the patient's condition was severe, hemodynamics was stable, breathing was independent, against the background of oxygen insufflation at a rate of 5 l/min, saturation 90%, body temperature 38 °C, volume of diuresis is reduced to 750 ml per day.

At the time of admission, the patient continued to receive basic immunosuppressive therapy. Mycophenolic acid was discontinued.

Chest X-ray showed signs of hyperhydration: fluid was detected in the left pleural cavity up to the level of the 8th rib. No infiltrative changes were detected in the visible parts of the lung tissue. Pulmonary pattern was diffusely enhanced due to the interstitial component.

According to laboratory investigations, we paid attention to significant leukocytosis up to 32.29 × 10^9/L, increased C-reactive protein (CRP) up to 352.3 mg/L, decreased hemoglobin level to 85 g/L, thrombocytopenia 26 × 10^9/L, high level of azotemia – creatinine 643 μmol/L, urea 27.4 mmol/L, in the general urine analysis: proteinuria 2.3 g/L, significant leukocyturia and bacteriuria, unchanged red blood cells 20–24–29 cells in the field of view.

Ultrasound examination: kidney transplant was located in the right iliac region, its contour is unclear in the lower third, approximate dimensions were 176 × 87 mm, the thickness of the parenchyma was 24 mm, increased echogenicity of II degree. Elements of the pyelocaliceal system: the cups of the upper group are expanded to 20 mm; a hyperechoic tubular structure is located in the projection of the upper cups – nephrostomy. In Doppler colour flow mapping (DCFM) mode, blood flow in the "vascular tree" of the graft was depleted at all levels. The resistive index at the level of the superior segmental artery was satisfactory. The middle and lower third of the graft were made of a hypoechoic mass with an indistinct contour and approximate dimensions of 79 × 67 × 73 mm; in the DCFM mode, vascular elements were identified in the structure of the mass.

Considering the above, the severity of the patient's condition was determined by the presence of graft neoplasm with impaired urodynamics and development of secondary pyelonephritis. In the somatic status, a differential diagnosis was made between urosepsis, paraneoplastic syndrome, and graft rejection. Ceftriaxone-based antibacterial therapy, disinfection therapy, and oxygen insufflation were empirically prescribed.

During the observation period, the patient's condition worsened, there were increased laboratory markers of inflammatory reaction.

According to radiography and chest computed tomography (CT) scan, negative dynamics were noted: marked increase in interstitial pulmonary edema (compared to the chest X-ray of November 11, 2021), clinically accompanied by hemoptysis (Fig. 1). In order to reduce systemic hyperhydration, an RRT session (long-term hemodialysis) through a central two-way venous catheter was performed.

Due to the growing phenomena of multiple organ failure, according to vital indications, urgent transplantectomy was performed (Fig. 2) on November 14, 2021.

Macroscopic description: the kidney was decapsulated, its dimensions were 140 × 110 × 90 mm. In the lower pole, there was a round tumor nodule without clear boundaries, about 70 mm in diameter, dense, yellowish-gray with whitish interlayers, homogeneous structure. The border of the cortical and medulla layers is not traceable, multiple confluent hemorrhages.

In the early postoperative period, transfusions of fresh frozen plasma, platelet concentrate, red blood cell mass were carried out, RRT (long-term hemodialysis) was resumed. Against the background of triple-drug antibacterial therapy (linezolid, meropenem, gentamicin), manifestations of systemic inflammatory reaction decreased: decreased CRP (114.10 mg/L) and

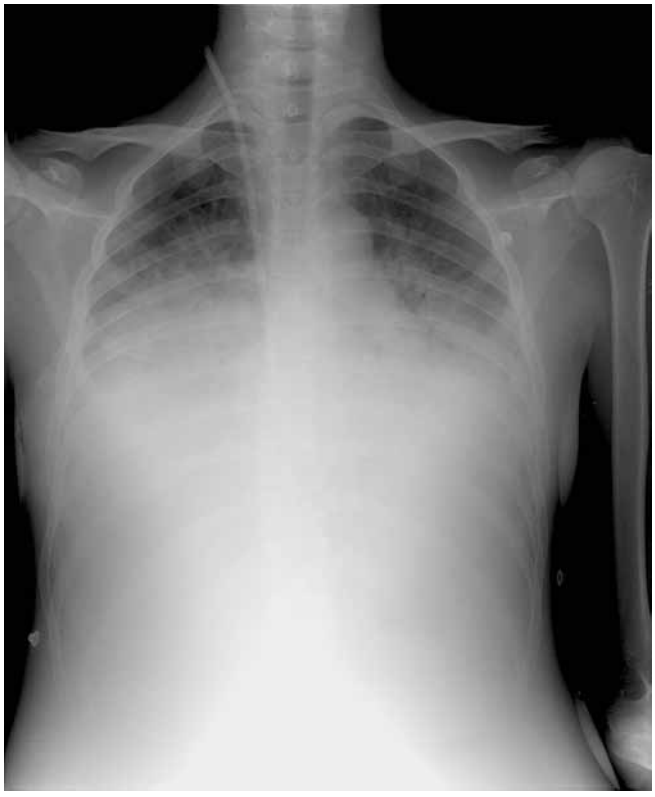

Fig. 1. Chest X-ray dated November 13, 2021

leukocytosis (14.34 × 10^9/L); high level of procalcitonin (68.4300 mcg/L) remained.

According to the results of urine culture conducted on November 16, 2021: Klebsiella pneumoniae ssp pneumoniae 1 × 10^6 cfu/mL, sensitivity to amikacin, gentamicin, and sulfamethoxazole / trimethoprim). Culture of wound discharge: Klebsiella pneumoniae ssp pneumoniae moderate growth, cross-sensitivity to the above-mentioned drugs was revealed. Blood culture – no microbial growth detected.

In the postoperative period, ultrasound detected no fluid accumulation in the graft bed.

On day 4 after the surgical intervention, the patient's condition worsened – in the form of febrile fever up to 39 °C, increase in leukocytosis up to 30.52 × 10^9/L, CRP up to 214 mg/l, despite ongoing antibacterial therapy. Abdominal and chest CT scans were conducted: CT signs of polyserositis (ascites, bilateral hydrothorax), small amount of blood in the pouch of Douglas, infiltration of the anterior abdominal wall in the hypogastric region, infiltration in the surgical intervention area – most likely, postoperative changes with the accession of inflammatory process. CT picture of alveolar-interstitial pulmonary edema.

In order to sanitize the focus of infection, for vital indications, emergency surgical intervention was performed – revision of the graft bed, laparotomy, sanitation and drainage of the abdominal cavity. As a result of revision in the graft bed, a liquid formation – an organized hematoma with signs of infection – was detected, serous peritonitis was detected in the retroperitoneal space. Cultures of the wound discharge: Klebsiella pneumoniae ssp pneumoniae abundant growth, same sensitivity.

In the postoperative period, fever regressed, leukocytosis reduced to 11.97 × 10^9/L, CRP to 101.9 mg/L. A mycological study of bronchoalveolar lavage (BAL) was carried out to determine sensitivity to antimycotics: Candida albicans 1 × 10^5 cfu/mL, sensitive to fluconazole, voriconazole. Therapy was adjusted according to the culture.

On the control chest X-ray conducted on November 22, 2021, compared to the X-ray conducted on November 17, 2021, there was still a decrease in the airiness of the lower parts of the lungs (no dynamics). Against this background, in the middle lung sections on both sides and in the lower lung sections on the right side, bilateral infiltration of lung tissue was determined, there was increasing severity of infiltration on the right side (negative dynamics).

On November 29, 2021, a morphological study of the removed kidney transplant was obtained: the tumor is represented by an infiltrate consisting mainly of small and medium-sized cells with irregularly shaped nuclei and light eosinophilic cytoplasm, a moderate amount of plasma cells (Fig. 3).

IHC study was performed to determine the immunophenotype of the tumor: atypical cells strongly expressed CD45, CD38, CD43, CD33, myeloperoxidase (Fig. 4). There was no expression of CD34, CD117, CD3, CD7, CD20, Pax-5, MuM.1, EBER, cytokeratins (pan-AE1/AE3) in the tumor cells (Fig. 5).

Reactions with antibodies to the light chains of kappa- and lambda immunoglobulins were performed, and

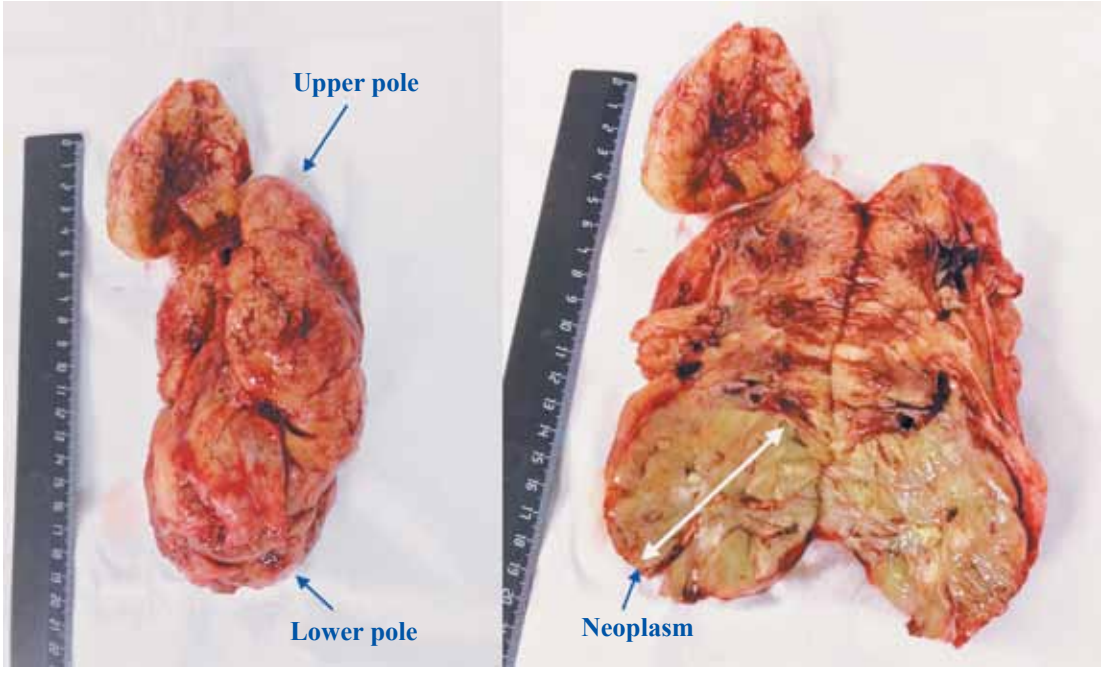

Fig. 2. Removed kidney graft with neoplasm

background staining was obtained. Ki-67 was not less than 60% (Fig. 6).

Thus, the tumor structure and phenotype are consistent with myeloid sarcoma (CD45+, CD38+, CD43+, CD33+, myeloperoxidase+, Ki-67 >60%).

Chest CT scan conducted on December 6, 2021: CT picture of increasing right-sided pleural effusion, pericardial effusion, minimal decrease in the severity of bilateral interstitial-alveolar changes, their extent is the same. The changes may correspond to manifestations of pulmonary interstitial-alveolar edema, manifestations of lymphoproliferative disorder; against this background, infection (bacterial/fungal) cannot be ruled out (Fig. 7).

Given the presence of bilateral infiltrative changes in the lungs, not regressing for a long time on the background of multidrug antibacterial, antifungal therapy, bronchoscopy was performed on December 7, 2021: diffuse catarrhal moderate endobronchitis. BAL examination was performed: bacteriological examination with determination of sensitivity to antibiotics – no growth was detected; determination of galactomannan antigen – the sample was positive (positivity index 4.974); cytolo-

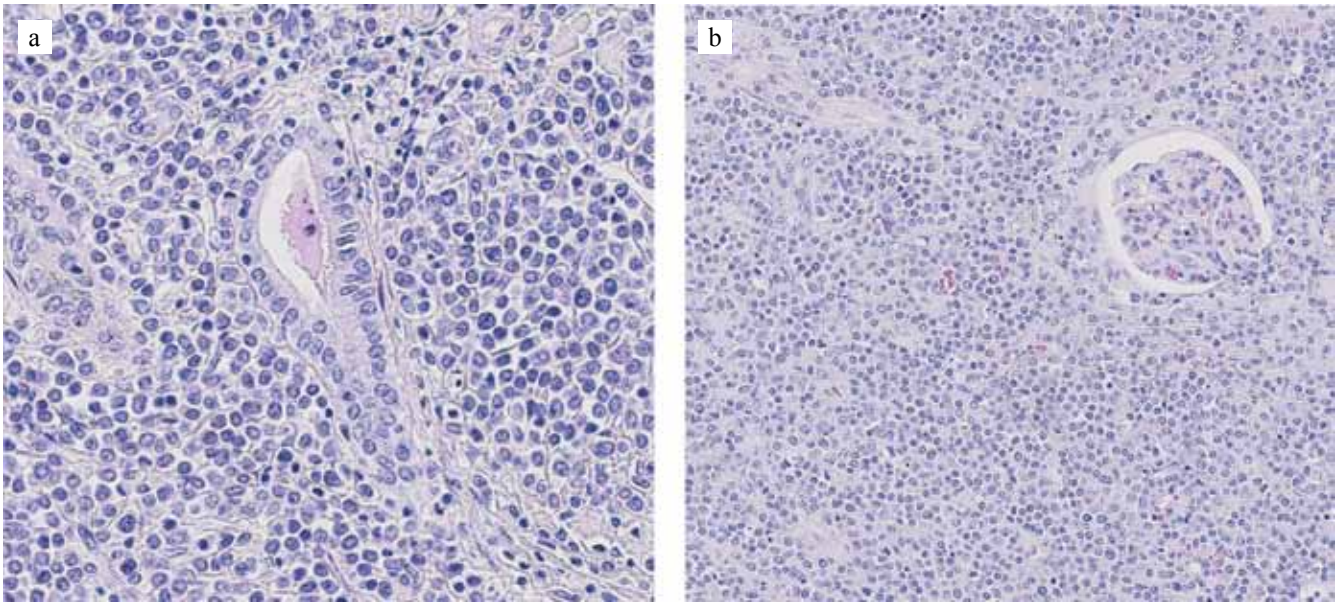

Fig. 3. Morphological picture of post-transplant lymphoproliferative disorder. H&E stain, magnification 630× (a), 400× (b)

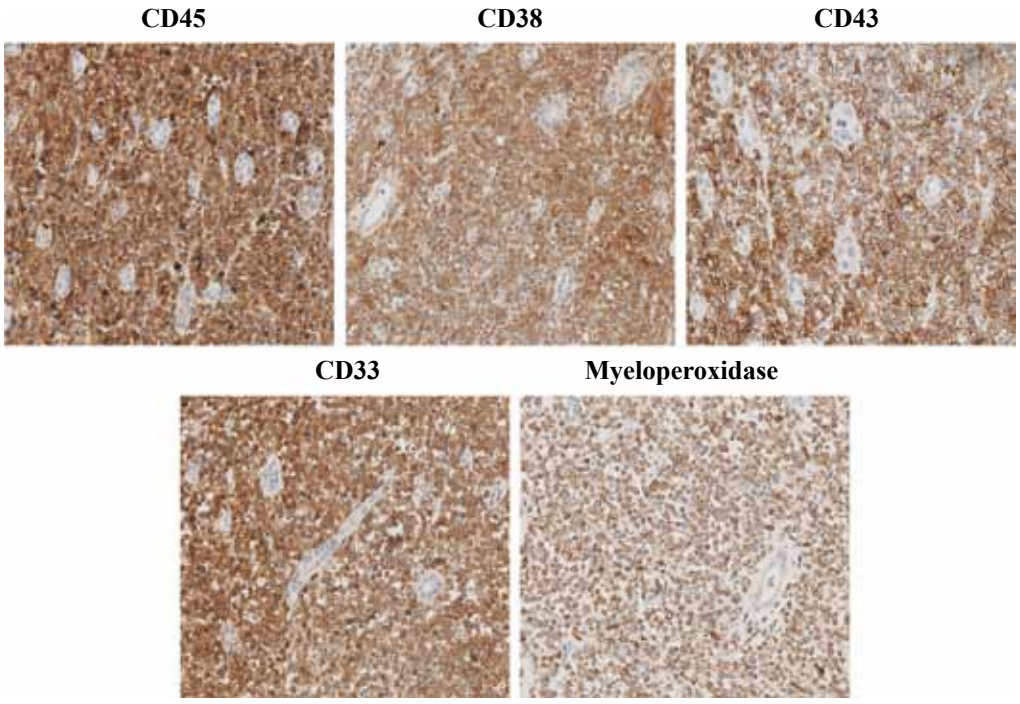

Fig. 4. IHC: atypical cells strongly express CD45, CD38, CD43, CD33, myeloperoxidase

gical examination of upper respiratory tract swabs – no evidence of malignant growth; microscopic examination for fungi – no fungal elements were detected during microscopy. Antifungal and antibacterial therapy was continued at the same level.

Chest CT scan of December 14, 2021: CT picture of pronounced positive dynamics of changes – resolved bilateral pleural effusion, regressed severity of pulmonary interstitial-alveolar edema. CT picture of bilateral peribronchial interstitial changes.

The hemogram test showed persistent anemia – decrease in hemoglobin to 64 g/L, normalization of platelet 344 × 10^9/L and white blood cell levels 7 × 10^9/L, no blasts.

Bone marrow trephine biopsy was performed: normocellular bone marrow, features of dysplasia in the granulocyte lineage (Fig. 8).

Myelogram: the presented bone marrow punctate preparations were normocellular, stromal fragments were filled with hematopoietic elements, without bone marrow

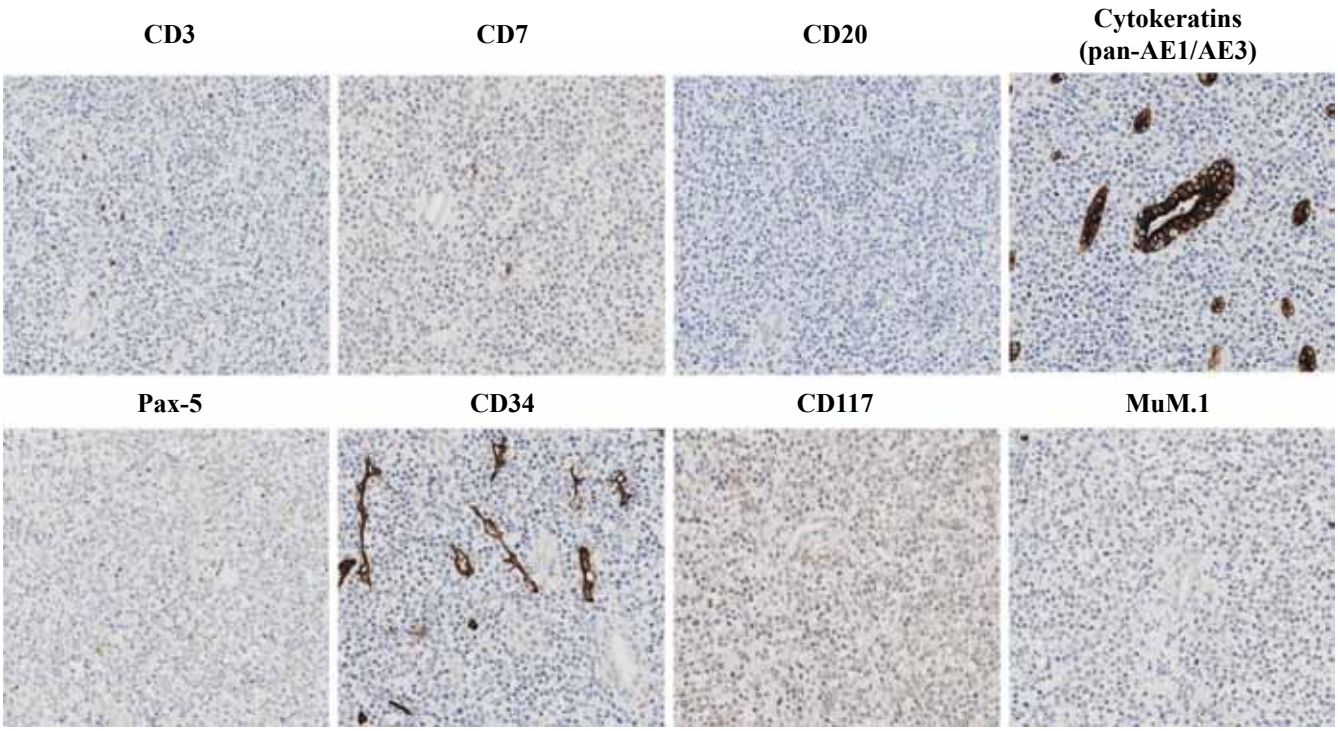

Fig. 5. IHC: atypical cells do not express CD34, CD117, CD3, CD7, CD20, Pax-5, MuM.1, cytokeratins (pan-AE1/AE3)

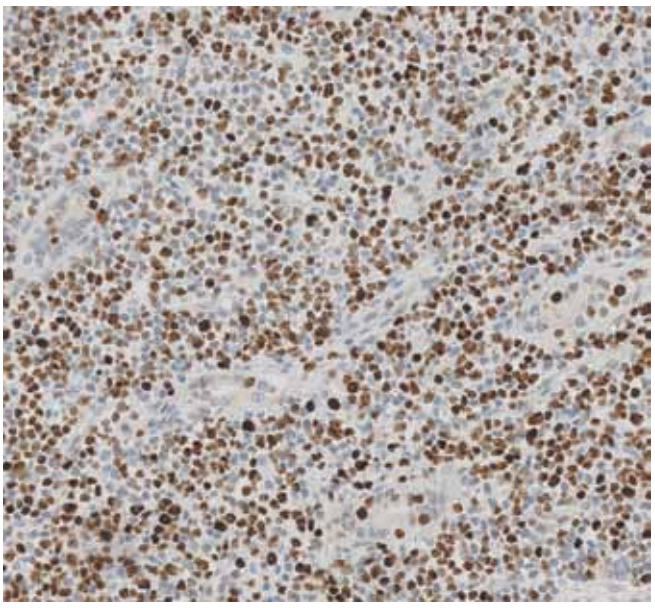

Fig. 6. Ki-67 >60%

lesions in myeloid sarcoma. Immunophenotyping of bone marrow cells – no pathology was detected. Karyotyping of bone marrow cells – no chromosomal pathology was detected. Molecular genetic markers of acute leukemia – no pathology was detected.

FISH analysis of X and Y chromosomes was not performed due to the donor's gender.

The patient was discharged from the transplant department of the Pavlov University on December 27, 2021 in a satisfactory condition, with positive dynamics in the form of improved well-being, normalized body temperature, increased hemoglobin level up to 100 g/L, decreased CRP up to 20.7 mg/L, pronounced positive dynamics in the form of resolved bilateral pleural effusion and regressed severity of pulmonary interstitial-alveolar edema. At present, the patient is receiving RRT (long-term hemodialysis) as planned. Guidelines for follow-up by an oncohematologist at the place of residence were given.

DISCUSSION

Given the complexity of screening for this pathology and the consequent high incidence of misdiagnosis, the diagnosis is often made in the later stages of the disease. Verification at early stages probably ensures a less severe course of this pathology.

From this clinical case, it is not possible to determine whether the disease is *de novo* or donor-derived, but the likelihood of this disease occurring should be considered at the donor stage.

If a hematopoietic tumor (CD45+) is suspected and T- and B-cell markers are absent, CD43 and myeloid markers (myeloperoxidase) should be included in the diagnostic panel.

Knowledge of epidemiological causes, pathogenesis, imaging features and treatment of malignant tumors in solid organ transplant recipients is a significant part of diagnostic screening at any stage of the post-transplant period.

CONCLUSION

From this clinical case, it is not possible to establish the nature of the disease – *de novo* or donor-derived. A 29-year-old patient was diagnosed with myeloid sarcoma of a kidney transplant with the development of paraneoplastic syndrome (anemia, leukemoid reaction, thrombocytopenic purpura, hypocoagulation), secondary pyelonephritis, sepsis, bilateral fungal pneumonia, increasing azotemia, and hyperhydration phenomena, which required emergency graft nephrectomy and resumption of long-term hemodialysis.

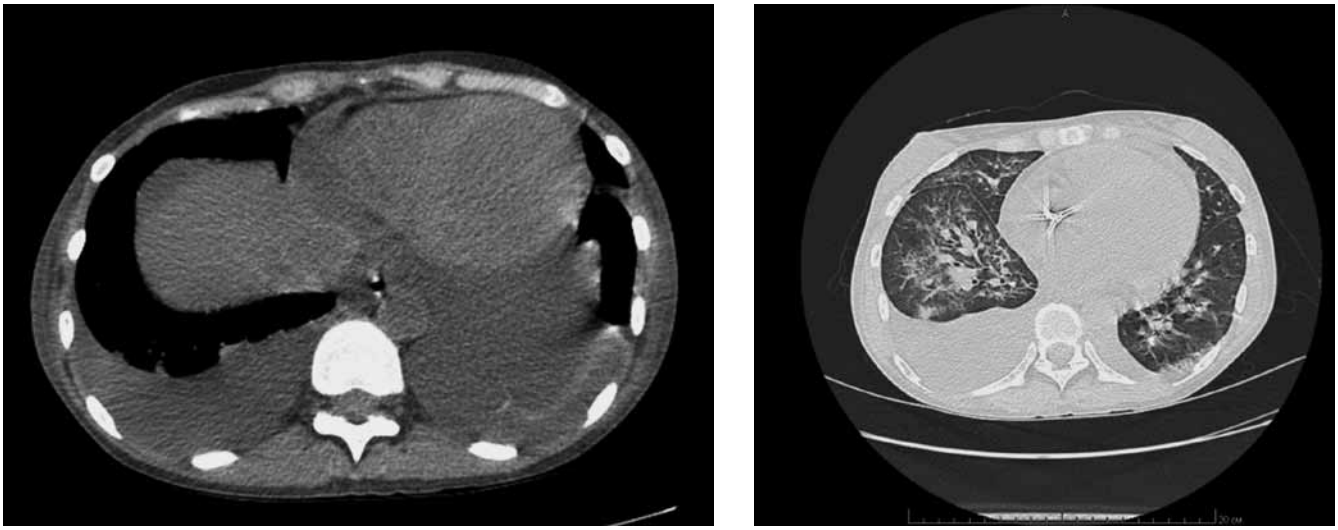

Fig. 7. Chest CT scan dated December 6, 2021

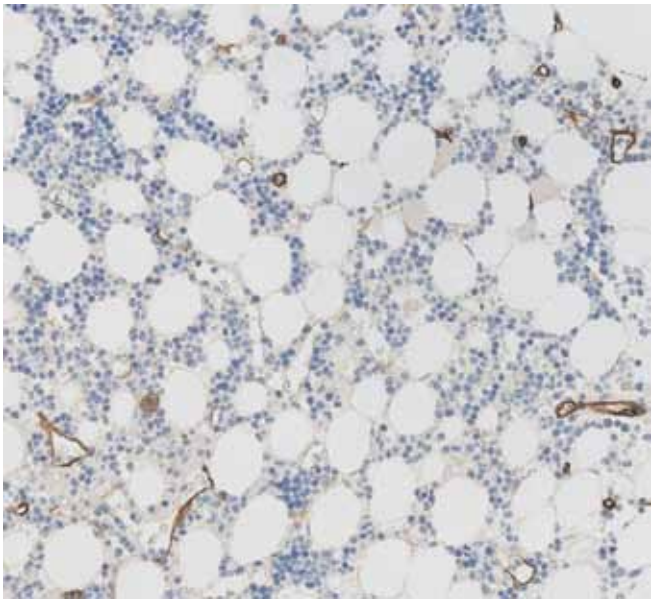

Fig. 8. Bone marrow trephine biopsy. The proportion of CD34+ cells is less than 2% of all karyocyte cells

An essential prerequisite for a successful kidney transplant outcome is communication between the center where the transplant was performed and the patients who underwent the operation. Late diagnosis of malignant tumors in a transplanted kidney in conditions where the stages of treatment and follow-up are disconnected, leads not only to graft loss but also jeopardizes the life of recipients.

The key to early detection of kidney transplant disease and provision of medical care in due time is prompt hospitalization in a specialized hospital. Successful management of such patients involves the work of a transplant multidisciplinary team.

The authors declare no conflict of interest.

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