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Disseminated intravascular coagulation following femoral nailing in a metastatic prostate carcinoma patient – A case report

Jeremy Wei Sern Lim^{*}, Wei Zhang, Derek Howard Park, Antony Xavier Rex Premchand

Department of Orthopaedic Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828, Singapore

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ABSTRACT

Introduction: Disseminated intravascular coagulation (DIC) is a rare condition that is known to affect patients with metastatic prostate adenocarcinoma. In an unsuspecting orthopaedic surgeon, DIC could lead to significant morbidity and mortality. This article highlights another such case and discusses management strategies to help improve clinical outcomes for these patients.

Case: A 70-year-old male with metastatic prostate adenocarcinoma underwent prophylactic intramedullary nailing of an impending right femur pathological fracture. Surgery was uneventful, however postoperatively he was haemodynamically unstable with heavily soaked dressings. Laboratory investigations revealed DIC. Supportive treatment and correction of coagulopathy were undertaken. Ketoconazole was also initiated by Urology Services to treat the underlying condition of metastatic prostate carcinoma. Unfortunately, the patient responded poorly and passed away.

Conclusion: DIC is rarely encountered in orthopaedic surgery, but carries significant morbidity and mortality risks. Patients with risk factors, in particular metastatic cancer, should be screened for non-overt pre-DIC state and coagulopathies corrected preoperatively. Initiating treatment of underlying condition can be considered preoperatively in established non-overt DIC. Operative technique can also be modified to minimise risk of fat or tumour emboli. Early recognition, prompt resuscitation and timely treatment of underlying condition may be able to improve the outcomes in these patients.

Introduction

Disseminated intravascular coagulation (DIC) is a systemic disorder involving the coagulation system, with simultaneous activation of procoagulatory cascade, fibrinolysis, and development of a consumption coagulopathy [23]. It may eventually result in shock, multiorgan dysfunction and death [23].

DIC is an acquired condition that is most commonly associated with malignancy and sepsis. It has been reported in up to 20% of patients with metastasized adenocarcinoma or lymphoproliferative disease [24]. Other causes include trauma, liver disease, pancreatitis, transfusion reactions, obstetric conditions, and surgery [24]. Regardless of cause, prognosis is grim [24].

Although rare, there are scattered case reports of DIC occurring after orthopaedic surgery [25–33], a significant number of which

^{*} Corresponding author.

E-mail addresses: jeremy.lim@mohh.com.sg (J.W.S. Lim), wei.zhang2@mohh.com.sg (W. Zhang), park.derek.howard@ktph.com.sg (D.H. Park), [premand.chand.antony.xr@ktph.com.sg](mailto:premchand.antony.xr@ktph.com.sg) (A.X.R. Premchand).

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occurred in the setting of known malignancy [28–33]. With improvement in treatment and increase in life expectancy of patients with malignancy, it is likely that orthopaedic surgeons will increasingly be managing patients with risk factors for this rare but potentially fatal complication. Preventive strategies, rapid recognition and prompt management are needed to limit morbidity and mortality associated with this condition.

We report a case of DIC in a patient with metastatic prostate cancer following prophylactic intramedullary nailing of an impending femur pathological fracture. We will also discuss management strategies for the orthopaedic surgeon.

Statement of informed consent

As our patient was unfortunately deceased, verbal consent was taken from a member of his family instead. His brother was informed that data concerning the patient would be submitted for publication for which he agreed.

Case presentation

A 70-year-old man with a known history of Gleason 9 metastatic prostate adenocarcinoma and chronic obstructive pulmonary disease (COPD) presented to the Emergency Department with dyspnoea, increased sputum production and severe right hip and lower back pain limiting ambulation. There was no history of prior trauma.

His prostate adenocarcinoma was first diagnosed in 2015 for which he underwent transurethral resection of the prostate (TURP) and bilateral orchidectomy in the same year. He was subsequently diagnosed with spinal bony metastasis of presumptive prostate origin for which he received radiotherapy to T6-T8 in 2017. He was on maintenance anti-androgen therapy with Bicalutamide for his metastatic prostate cancer at point of admission.

On examination, his right hip was tender on movement with reduced range of movement due to pain. There was no associated warmth or swelling of his right hip. He also had rhonchi and bibasal crepitations in both lungs.

X-rays of his pelvis and right femur showed bony metastasis throughout the pelvis and right proximal femur [Fig. 1]. Laboratory investigations were significant for raised inflammatory markers – white blood cell count (WBC) of $17.71 \times 10^9/L$ and C-reactive protein (CRP) of 56.3 mg/L.

He was diagnosed with exacerbation of COPD and right hip pain secondary to bony metastasis and admitted to the Department of Palliative Medicine. His COPD exacerbation was treated with Intravenous Augmentin and oral prednisolone. An MRI of his right hip was performed which showed extensive metastatic involvement of the region of the head, neck, trochanters and proximal shaft of the right femur without pathological fractures [Fig. 2], and a consult was made to Orthopaedic Surgery for further management of his symptomatic right hip metastasis.

A Mirel's score of 10 was calculated for the patient [4] and decision to offer prophylactic fixation was made after discussion with a tumour surgeon. After detailed discussion of risk and benefits, patient consented to the surgery. His preoperative haematological



Fig. 1. X-ray showing sclerotic bony metastasis in the right proximal femur and adjacent pelvis.

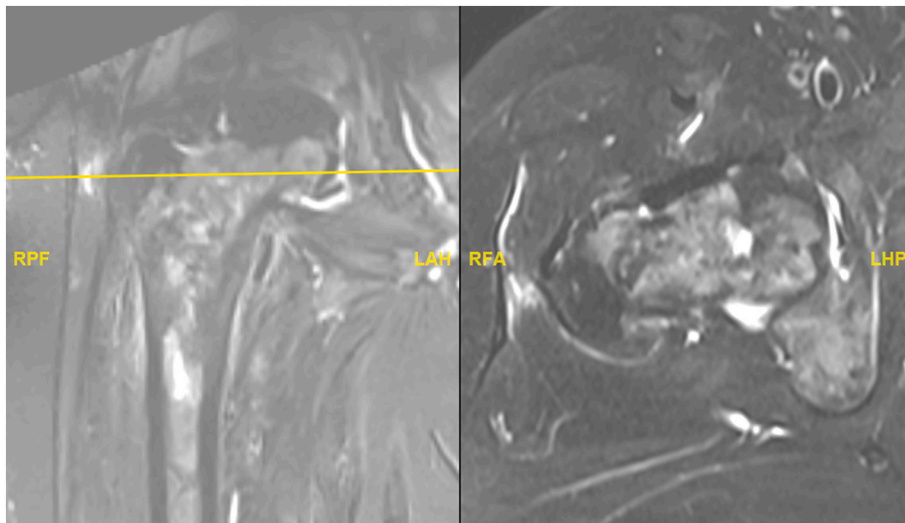


Fig. 2. MRI of patient's right hip showing extensive metastatic involvement of the region of the head, neck, trochanters and proximal shaft of the right femur.

investigations were normal, as follows: international normalised ratio (INR) of 1.0 prothrombin time (PT) 10.7 s activated partial thromboplastin time (aPTT) of 20.8 s, Platelet count $175 \times 10^9/L$ and haemoglobin level 12.1 g/dL.

The patient subsequently underwent prophylactic surgical fixation of his right hip with a long TFN-ADVANCED Proximal Femoral Nailing System (TFNA) from DePuy Synthes under general anaesthesia and femoral nerve block. Standard skin incisions were performed. After insertion of guidewire and opening ream, the medullary canal was sequentially reamed with flexible reamers starting from 8.5 mm diameter, increasing in 0.5 mm increments to 13.5 mm. A 380 mm size 12 TFN-A nail was inserted. A size 95 mm blade was then inserted. Cement augmentation into the femoral head through the TFNA blade was also performed to improve fixation stability in view of extensive tumour involvement of the femoral head. Distal interlocking screws were then inserted. Layered closure was performed and surgical staples were used to close skin. Postoperative radiographs are shown in Fig. 3.

Total surgical time was 2 h and 30 min. The estimated intra-operative blood loss was 600mls. Patient remained stable intra-operatively, and was transferred back to the general ward after a period of monitoring in the recovery area.

Shortly after arriving back to the ward, the patient became confused and was haemodynamically unstable. Examination revealed that he had heavily blood-soaked surgical dressings. The patient was transferred to the surgical intensive care unit (SICU) and intubated in view of persistent haemodynamic instability. Laboratory results showed a haemoglobin count of 7.0 g/dL, platelet count of $123 \times 10^9/L$, aPTT of 132.2 s and PT of 16.7 s. D-dimer was elevated at >35.20 mg/L, and fibrinogen was decreased at 0.61 g/L.

A diagnosis of DIC was made after discussion with intensivists and supportive management with transfusion of blood products was

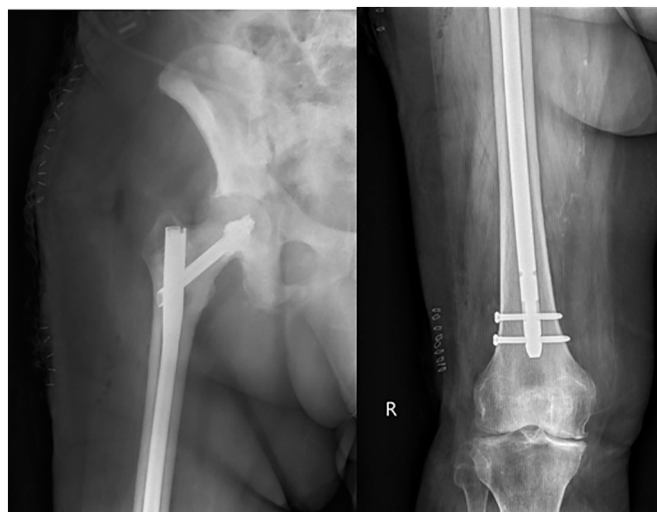


Fig. 3. Postoperative radiograph after prophylactic surgical fixation of the right femur with the TFN-A nail and cement augmentation.

Study	Patient demographic	Significant past medical history	Preoperative haematological workup	Orthopaedic procedure	Presentation	Management	Outcome
Hassmann et al. (1974) [25]	13 Female	Mild congenital myopathy	Normal	Surgical correction of thoracic myopathic scoliosis with use of Harrington instrumentation and autologous bone graft assisted spinal fusion	Diffuse oozing from wound bed followed by hypotension and cardiac arrest 90 minutes into surgery	Blood product transfusion ICU support	Coagulation profile normalised POD 5. Full recovery
Demirjian et al. (1974) [27]	60 Female	Unknown	Unknown	Open reduction and internal fixation of right femur periprosthetic fracture nonunion with use of autologous iliac crest bone grafts	Diffuse oozing during final 45 min of operation. Persistent incision site oozing first. 12 h postop	Blood product transfusion	Coagulation profile normalised POD 7. Full recovery
Demirjian et al. (1974) [27]	22 Male	Nil	Normal Single dose low molecular weight dextran given preoperatively as thromboprophylaxis	Left revision total hip replacement	No hypotension Diffuse oozing resulting in 9 L blood loss intraoperatively	Blood product transfusion	Coagulation profile normalised POD 5. Full recovery
Demirjian et al. (1974) [27]	71 Male	Unknown	Slightly prolonged bleeding time attributed to aspirin intake Taking aspirin 600 mg BD	Left total hip replacement	Significant postoperatively blood loss via surgical drain (1.2 L in 6 h)	Blood product transfusion	Coagulation profile normalised POD 5. Full recovery
Raphael et al. (1982) [26]	26 Female	Paraplegia from childhood T6 level spinal injury	Normal	Surgical correction of thoracic scoliosis with use of Harrington instrumentation and autologous bone graft assisted spinal fusion	Acute onset diffuse oozing from wound bed with decortication of bone to obtain graft material followed by hypotension	Blood product transfusion	Coagulopathy resolved by POD 2. Full recovery
Raphael et al. (1982) [26]	13 Female	Multiple osteochondroma	Normal	Surgical correction of thoracic scoliosis with use of Harrington instrumentation and autologous bone graft assisted spinal fusion	Acute onset diffuse oozing with decortication of bone to obtain graft material requiring 14 units of transfusion. Heavy postoperative bleeding first 24 h	Blood product transfusion	Coagulopathy resolved by POD 2. Full recovery
Nyska et al. [1987] (28)	70 Male	Metastatic adenocarcinoma with metastasis to bilateral proximal femur	Prolonged thrombin time	Bilateral ender's nailing for fixation of left hip pathological fracture and right hip impending pathological fracture	Sudden onset Hypotension and profuse oozing few hours into surgery	Blood, clotting product transfusion, and crystalloids	Clotting profile normalised within 8 hours. Acute tubular necrosis and death POD 9
Nyska et al. [1987] (28)	68 Female	Metastatic breast cancer with pathological right hip fracture	Prolonged thrombin time Slightly raised partial thromboplastin time	Richard's compression nailing and plating of pathological right hip pressure	Sudden onset hypotension, profuse oozing and cardiac arrest intraoperatively	Not specified	Kidney failure and death 24 h postoperatively
Olsen et al. (1990) (31)	58 Male	Metastatic prostate cancer	Normal	Nailing of pathological humerus fracture	Profuse bleeding postoperatively	Blood product and clotting	Death POD 12

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Study	Patient demographic	Significant past medical history	Preoperative haematological workup	Orthopaedic procedure	Presentation	Management	Outcome
Persson et al [1994] (29)	53 Female	Metastatic breast with metastasis to right femur cancer Sarcoidosis	Low molecular weight heparin 5000 U SC preoperatively	Prophylactic nailing of impending right femur pathological fracture	Sudden onset transient hypotension and hypoxia during medullary reaming. Postoperative decline into shock	factor transfusion ICU	Death few hours postoperatively
Persson et al [1994] (29)	74 Male	Metastatic prostate cancer with generalised skeletal metastasis Hypertension Ischaemic heart disease	Not specified	Prophylactic nailing of impending right femur pathological fracture	Recurrent sudden onset transient hypotension during reaming through tumour, with profuse bleeding (total 6 L) from bone marrow canal	Blood product and clotting factor transfusion. ICU support	Stabilised and transferred to general ward POD 2, but deterioration and death 2 weeks postoperatively
Ward et al. (1995) [30]	66 Male	Metastatic prostate cancer	Not specified	Prophylactic nailing of impending femur pathological fracture	Hypotension and profuse oozing during insertion of distal locking screw	Blood product and clotting factor transfusion	Death 5 months postoperatively
Rafiq et al. (2015) [33]	62 Male	Metastatic prostate cancer	normal	Decompression and instrumentation thoracolumbar spine for pathological T6 and L1 fracture with cord compression	Profuse bleeding intraoperatively	Blood product and clotting factor transfusion	Coagulopathy resolved POD 5. Full recovery
You et al. (2020) [32]	85 Male	Hypertension Hyperlipidemia Metastatic prostate cancer with extensive bone metastasis and disseminated carcinomatosis of bone marrow	Abnormal international normalised ratio (1.4) Low platelet count ($51 \times 10^9/L$) Low haemoglobin (80 g/L)	Prophylactic nailing of impending left femur pathological fracture	Excessive incision site bleeding 1 h postoperatively	Blood product and clotting factor transfusion ICU support	Coagulopathy resolved POD 3 Death 6 months postop

initiated. The patient received a total of 7 units of packed red cells, 4 units of 200mls 5% albumin, 2 units of cryoprecipitate, and 3 units of fresh frozen plasma (FFP). Urology was consulted and a dose of oral Ketoconazole 200 mg was administered to the patient. Despite these efforts, the patient's condition continued to deteriorate. In view of a guarded prognosis, the patient was placed on comfort measures and passed away the following day.

Discussion

DIC is a rarely encountered complication in orthopaedic surgery. A search of literature identified 15 cases of intraoperative and postoperative DIC occurring in orthopaedic surgery including our own [Table 1] [25–33]. Its incidence varies with underlying predisposing risk factors [24]. Malignancy is an important risk factor in the setting of orthopaedic surgery. Of the 15 cases in reported literature, 9 occurred in surgery for metastatic pathological fractures, including our case [28–32] [Table 1]. In a study with 30 patients who were operated on for pathological hip fractures secondary to bone metastasis over 3 years at an institution in Israel, 2 patients developed DIC [28]. DIC has also been reported in patients without known risk factors undergoing elective spine surgery and complex hip arthroplasty, presumptively with long surgical time and intraoperative blood loss [25–27] [Table 1].

Although uncommon in orthopaedics surgery, DIC might be more common than one would suspect in the setting of certain metastatic disease. In patients with metastasized adenocarcinoma or lymphoproliferative disease, the incidence of DIC can be as high as 20% [24]. Prostate adenocarcinoma is a common malignancy amongst men and has a tendency for metastasis to the bones [34,35]. The incidence of subclinical DIC in metastatic prostate cancer patients can be as high as 24–40% [36]. Sepsis and severe trauma are other commonly encountered predisposing factors [24].

Although rare in orthopaedics surgery, DIC carries a high mortality rate. Of the 9 patients that developed DIC after fixation of

pathological fractures, 6 passed away within 2 weeks post surgery [28–33].

DIC results from widespread activation of clotting pathways, leading to excessive generation and disseminated deposition of fibrin clots in small and midsize vessels [5]. This can then cause multi organ failure by ischaemic necrosis [5]. During this disseminated clotting process, platelets and clotting factors are consumed, leading to haemorrhagic complications at the same time [5]. DIC not a disease in itself, but rather secondary to a wide variety of disease states, with the basic process involving the triggering of physiologic clotting mechanism that propagates and becomes systemic and pathological [24,37]. Triggering mechanism varies, and can include cell membrane components of microorganisms or exotoxins in the setting of sepsis [37], cancer procoagulant proteins in the setting of malignancy [2], and release of endothelial cell thrombomodulin and thromboplastin in the setting of trauma [38]. Hypotension and shock follow DIC via several pathways: formation of potent vasodilatory bradykinins, blood loss, and reduced venous return and cardiac output from the obstruction of splanchnic and pulmonary vessels [39]. Shock can in turn trigger DIC through academia and hypoxaemia induced endothelial damage and cell damage, with release of procoagulant cell phospholipids [40]. Thus, unless promptly halted, DIC and shock propagate each other and can become refractory once established [40].

In the context of orthopaedic surgery, fat embolism and release of tumour emboli can trigger DIC [41]. Fat emboli released from fractures, medullary reaming and cementing occlude small vessels, producing stasis and cellular hypoxic injury, predisposing to coagulation [41]. Fat emboli in plasma are broken down by lipases into free fatty acids, which further damages endothelial lining cells and potentially triggering the coagulation cascade [41]. Fat embolism also directly exacerbates the multiorgan injury and hypotension seen in DIC via occlusion of vessels and vasodilatory cytokines such as tumour necrosis factor alpha [29,41]. Manipulation of sites of metastasis in orthopaedic surgery, such as reaming through an impending pathological fracture or decompressing tumour metastasis to the spine, can also release tumour emboli into the systemic circulation. Tumour cells in these emboli express tissue factor, which triggers coagulation cascade [42]. Decortication of bone to obtain graft material, as is frequently performed in spine surgeries, has been postulated to expose massive raw surface for contact activation of clotting system [26]. Perioperative hypothermia [43] and hypotension [39] may also contribute to DIC in the surgical patient. In our case, a combination of procoagulatory state of malignancy, as well as fat and tumour emboli released during cementing and reaming likely resulted in the development of DIC.

Acute DIC is a clinicolaboratory diagnosis. In the surgical patient, DIC should be suspected in at risk patients with sudden onset profuse surgical bed bleeding [25–30,33], intraoperative hypotension [25,26,28–30], and excessive postoperative bleeding [27,31–32]. They may subsequently develop ischaemic organ failures from thrombotic complications, such as kidney failure [28]. Coagulation tests aid diagnosis and provide an indication of severity of coagulation pathway activation and consumption [44]. Typical laboratory findings include thrombocytopenia or clear downtrending platelet count, reduced fibrogen level, prolonged partial thromboplastin time (APTT) and elevated fibrin-related markers such as D-dimer and fibrinogen-degradation product (FDP) [44,46–48]. Prothrombin time is prolonged in 50% of the time in patients with DIC [46]. Guidelines recommend use of scoring systems, such as the International Society of Thrombosis and Hemostasis - Scientific and Standardisation Subcommittee (ISTH-SSC) score, to facilitate definitive diagnosis [44,45]. This should however occur concurrently with treatment and stabilisation.

An important condition to identify in preoperative patients with metastatic malignancy is non-overt (impending) DIC. Although patients in non-overt DIC may not manifest active excessive bleeding, clotting, hypotension or organ failure seen in over DIC, they have a higher risk of mortality and instituting early treatment reduces this increased mortality rate [50,51]. In one study, mortality at 28 and 90 days in non-overt DIC patients managed with early treatment was reduced to 25.7% and 24.6% respectively compared to 40.9% and 51.8% respectively in placebo group [51]. Non-overt DIC is characterised by abnormal global coagulation laboratory tests such as platelet count, PT, APTT and D-dimer [50]. Diagnosis can be established with the modified ISTH criteria [50].

The foundation of DIC treatment lies in treating underlying disorder as well as supportive therapies to control abnormal coagulation [44]. Management of DIC should start even before surgery with the screening of at-risk patients for coagulation abnormalities and the identification of patients already in non-overt DIC. Any abnormalities should be corrected before proceeding to surgery [32]. We suggest that for patients who are already in non-overt DIC, treatment for underlying conditions, such as the use of anticancer drugs in malignant disease, should be considered prior to surgery to reduce risk acute overt DIC [44,52]. Preoperative hematology consult should also be considered for help in correction of coagulopathy. In the context of metastatic prostate cancer, hormonal therapy such as ketoconazole [14,15] or Degarelix [18] have been used to treat DIC successfully. Chemotherapy with Docetaxel [19] or mitoxantrone [22], and radiopharmaceutical therapy with strontium-89 [54] or Samarium 153 [53] have also been shown to be effective at treating DIC. However, in the surgical patient, these therapies may have detrimental effects on wound healing [55].

Intraoperatively, surgical techniques to minimise fat and tumour embolism be employed [56–60]. These include tumour bed curettage and medullary canal suction prior to reaming and implant insertion to reduce tumour load and medullary fatty marrow content [29], as well as techniques to reduce intramedullary pressures [29,56–60]. Intramedullary reamed nailing elevates intramedullary pressure and causes extravasation of intramedullary contents into the circulation system, resulting in embolization [56,57]. Indeed, onset of DIC coincided with intramedullary reaming in several reported cases [29]. Roth et al. showed that maximum intramedullary pressure levels and duration were higher during reaming of the unbroken femur being stabilised prophylactically for impending pathologic fracture are higher than those during reaming of fractured femurs, and can be reduced by venting [56]. Use of irrigation and suction has also been shown to reduce intramedullary pressure and fat embolism [57,58]. Using smaller advancing force at higher drill speeds also minimise the rise in intramedullary pressure during reaming [59,60]. When performing cemented arthroplasty, forgoing the use of cement restrictor can be considered to reduce rise in intramedullary pressure for high risk patients [29].

Hypothermia should be avoided as much as possible with the use of warming blankets, warmed fluid infusions, and control of operation theatre temperature [43]. Patient should be adequately filled and blood pressure tightly controlled intraoperatively to avoid prolonged periods of hypotension [39]. Diagnosis of DIC should be considered and coagulation studies promptly performed when there

is unexplained intraoperative hypotension or profuse surgical bed bleeding. Supportive measures with resuscitation, blood product transfusion and correction of coagulation should then be initiated promptly.

Postoperatively, patients at risk of development of DIC should be closely monitored for surgical site bleeding and hemodynamic instability. Early recognition, prompt resuscitation, correction of coagulopathy as well as treatment of underlying predisposing condition should be initiated with a multidisciplinary team approach. Serial laboratory investigations should also be performed to monitor progression of DIC and development of any organ failure, with appropriate supportive therapy.

Conclusion

DIC is rarely encountered in orthopaedic surgery, but carries significant morbidity and mortality risks. Patients with risk factors, in particular metastatic cancer, should be screened for non-overt pre-DIC state and coagulopathies corrected preoperatively. Initiating treatment of underlying condition can be considered preoperatively in established non-overt DIC. Operative technique can also be modified to minimise risk of fat or tumour emboli. Early recognition, prompt resuscitation and timely treatment of underlying condition may be able to improve the outcomes in these patients.

References

- [2] T. Wang, Z. Ding, B. Ni, J. Wang, J. Wang, Amplification of multiple receptor tyrosine kinase pathways in a patient with metastatic castration-resistant prostate cancer with disseminated intravascular coagulation (DIC), *ARC J. Hematol.* 2 (1) (2017) 16–22.
- [4] H. Mirels, Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures, *Clin. Orthop. Relat. Res.* 249 (1989) 256–264.
- [5] A. Venugopal, Disseminated intravascular coagulation, *Indian J. Anaesth.* 58 (5) (2014) 603–608.
- [14] F.C. Lowe, W.J. Somers, The use of ketoconazole in the emergency Management of Disseminated Intravascular Coagulation due to metastatic prostatic cancer, *J. Urol.* 137 (5) (1987) 1000–1002.
- [15] M.R. Litt, W.R. Bell, H.A. Lepor, Disseminated intravascular coagulation in prostatic carcinoma reversed by ketoconazole, *JAMA* 258 (1) (1987) 1361–1362.
- [18] S.Y. Ong, J. Taverna, C. Jockerst, T.ENZLER, E. Hammode, E. Rogowitz, M.R. Green, H.M. Babiker, Prostate cancer-associated disseminated intravascular coagulation with excessive fibrinolysis treated with degarelix, *Case Rep. Oncol. Med.* (2015) 1–6 (212543).
- [19] S. Keskin, M. Ekenel, M. Basaran, S. Bavbek, Successful use of docetaxel for emergency treatment of disseminated intravascular coagulation due to hormone-refractory metastatic prostate cancer, *J. Oncol. Sci.* 3 (2) (2017) 81–83.
- [22] M.R. Smith, Successful treatment with mitoxantrone chemotherapy of acute disseminated intravascular coagulation due to metastatic androgen independent prostate cancer, *J. Urol.* 163 (1) (2000) 248.
- [23] F.B. Taylor Jr., C.H. Toh, W.K. Hoots, H. Wada, Levi M scientific subcommittee on disseminated intravascular coagulation (DIC) of the international society on thrombosis and haemostasis (ISTH) towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation, *Thromb. Haemost.* 86 (2001) 1327–1330.
- [24] M. Levi, H. Ten Cate, Disseminated intravascular coagulation, *N. Engl. J. Med.* 341 (8) (1999) 586–592.
- [25] G.C. Hassmann, H.A. Keim, Disseminated intravascular coagulation (DIC) in orthopedic surgery. Case report and review of literature, *Clin. Orthop. Relat. Res.* 103 (1974) 118–132.
- [26] B.G. Raphael, H. Lackner, G.L. Engler, Disseminated intravascular coagulation during surgery for scoliosis, *Clin. Orthop. Relat. Res.* 162 (1982) 41–46.
- [27] Z. Demirjian, M. Sara, D. Stulberg, W.H. Harris, Disseminated intravascular coagulation in patients undergoing orthopedic surgery, *Clin. Orthop. Relat. Res.* 102 (1974) 174–180.
- [28] M. Nyska, B. Klin, J.Y. Margulies, A. Fast, Y. Floman, Disseminated intravascular coagulopathy in patients with cancer undergoing operation for pathological fractures of the hip, *Int. Orthop.* 11 (3) (1987) 179–181.
- [29] E.V. Persson, H.C. Bauer, Sudden hypotension and profuse bleeding during intramedullary nailing of the femur in cancer patients. A report of two cases, *Acta Orthop. Scand.* 65 (5) (1994 Oct) 564–567.
- [30] W.G. Ward, A.A. Hosseini, Disseminated intravascular coagulopathy (DIC) complicating intramedullary fixation of impending femur fracture from metastatic prostate cancer, *Orthopedics* 18 (11) (1995) 1115–1118.
- [31] S.A. Olson, W.G. Humphreys, W.C. Allen, Disseminated intravascular coagulation complicating Ender's nailing, *Clin. Orthop. Relat. Res.* 256 (1990) 242–244.
- [32] D.Z. You, J.K. Kendal, P. Duffy, M.J. Monument, P.S. Schneider, Acute disseminated intravascular coagulation after prophylactic nailing of the femur in a patient with metastatic prostate cancer: a case report, *JBJS Case Connect.* 10 (1) (2020), e0370.
- [33] M. Rafiq, J.D. Tobias, Intraoperative disseminated intravascular coagulation during thoracolumbar decompression in a patient with metastatic carcinoma of the prostate: etiology, diagnosis, and treatment, *J. Med. Cases.* 6 (9) (2015) 426–429.
- [34] G. Attard, C. Parker, R.A. Eeles, F. Schroder, S.A. Tomlins, I. Tannock, C.G. Drake, J.S. de Bono, Prostate cancer, *Lancet* 387 (10013) (2016) 70–82.
- [35] L. Bubendorf, A. Schopfer, U. Wagner, G. Sauter, H. Moch, N. Willi, T.C. Gasser, M.J. Mihatsch, Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients, *Hum. Pathol.* 31 (5) (2000) 578–583.
- [36] A.S. Adamson, J.L. Francis, R.O. Witherow, M.E. Snell, Coagulopathy in the prostate cancer patient: prevalence and clinical relevance, *Ann. R. Coll. Surg. Engl.* 75 (2) (1993) 100–104.
- [37] M. Franchini, G. Lippi, F. Manzato, Recent acquisitions in the pathophysiology, diagnosis and treatment of disseminated intravascular coagulation, *Thromb. J.* 4 (2006) 4.
- [38] M. Hayakawa, Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype, *J. Intensive Care* 5 (2017) 14.
- [39] R.A. Pixley, R. De La Cadena, J.D. Page, N. Kaufman, E.G. Wyshock, A. Chang, F.B. Taylor Jr., R.W. Colman, The contact system contributes to hypotension but not disseminated intravascular coagulation in lethal bacteremia. In vivo use of a monoclonal anti-factor XII antibody to block contact activation in baboons, *J. Clin. Invest.* 91 (1) (1993) 61–68.
- [40] T.N. Bell, Disseminated intravascular coagulation and shock. multisystem crisis in the critically ill, *Crit. Care Nurs. Clin. North Am.* 2 (2) (1990) 255–268.
- [41] J.P. Jones Jr., Fat embolism, intravascular coagulation, and osteonecrosis, *Clin. Orthop. Relat. Res.* 292 (1993) 294–308.
- [42] S. Sallah, J.Y. Wan, N.P. Nguyen, L.R. Hanrahan, G. Sigounas, Disseminated intravascular coagulation in solid tumors: clinical and pathologic study, *Thromb. Haemost.* 86 (3) (2001) 828–833.
- [43] D.L. Carden, R.M. Novak, Disseminated intravascular coagulation in hypothermia, *JAMA* 16; 247 (15) (1982) 2099.
- [44] Hideo Wada, Takeshi Matsumoto, Yoshiki Yamashita, Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines, *J. Intensive Care* 2 (1) (2014) 15.
- [45] F.B. Taylor, C.H. Toh, W.K. Hoots, H. Wada, M. Levi, Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation, *Thromb. Haemost.* 86 (2001) 1327–1330.
- [46] R. Bick, Disseminated intravascular coagulation: objective clinical and laboratory diagnosis, treatment, and assessment of therapeutic response, *Semin. Thromb. Hemost.* 22 (1996) 69–88.

- [47] M. Levi, C.H. Toh, J. Thachil, H.G. Watson, Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Committee for Standards in Haematology, Br. J. Haematol.* 145 (2009) 24–33.
- [48] D. Prisco, R. Paniccia, F. Bonechi, I. Francalanci, R. Abbate, G.F. Gensini, Evaluation of new methods for the selective measurement of fibrin and fibrinogen degradation products, *Thromb. Res.* 56 (1989) 547–551.
- [50] J.H. Lee, J. Song, Diagnosis of non-overt disseminated intravascular coagulation made according to the international society on thrombosis and hemostasis criteria with some modifications, *Korean J. Hematol.* 45 (4) (2010 Dec) 260–263.
- [51] KyberSept investigators, J. Kienast, M. Juers, C.J. Wiedermann, J.N. Hoffmann, H. Ostermann, R. Strauss, H.-O. Keinecke, B.L. Warren, S.M. Opal, Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation, *J. Thromb. Haemost.* 4 (2006) 90–97.
- [52] I. Duran, I.F. Tannock, Disseminated intravascular coagulation as the presenting sign of metastatic prostate cancer, *J. Gen. Intern. Med.* 21 (11) (2006) C6–C8.
- [53] A. Ruffion, A. Manel, C. Valignat, J.G. Lopez, O. Perrin-Fayolle, P. Perrin, Successful use of samarium 153 for emergency treatment of disseminated intravascular coagulation due to metastatic hormone refractory prostate cancer, *J. Urol.* 164 (3, Part 1) (2000) 782.
- [54] A.L. Paszkowski, D.J. Hewitt, A. Taylor, Disseminated intravascular coagulation in a patient treated with strontium-89 for metastatic carcinoma of the prostate, *Clin. Nucl. Med.* 24 (1999) 852.
- [55] Wyatt G. Payne, Deepak K. Naidu, Chad K. Wheeler, David Barkoe, Marni Mentis, R. Emerick Salas, David J. Smith, Martin C. Robson, Wound healing in patients with cancer, *Eplasty* 8 (2008), e9.
- [56] S.E. Roth, M.M. Rebello, H. Kreder, C.M. Whyne, Pressurization of the metastatic femur during prophylactic intramedullary nail fixation, *J. Trauma* 57 (2) (2004 Aug) 333–339.
- [57] P.N. Smith, A. Leditschke, D. McMahon, R.R. Sample, D. Perriman, A. Prins, T. Brüssel, R.W. Li, Monitoring and controlling intramedullary pressure increase in long bone instrumentation: a study on sheep, *J. Orthop. Res.* 26 (10) (2008 Oct) 1327–1333.
- [58] R.P. Pitto, M. Koessler, J.W. Kuehle, Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty. a prospective, randomized clinical trial, *J. Bone Joint Surg. Am.* 81 (1999) 831–843.
- [59] C.A. Muller, J. Green, N.P. Sudkamo, Physical and technical aspects of intramedullary reaming, *Injury* 37S (2006) S39–S49.
- [60] C. Muller, R. Frigg, U. Pfister, Effect of flexible drive diameter and reamer design on the increase of pressure in the medullary cavity during reaming, *Injury* 24 (Suppl 3) (1993) S40–S47.